Mar-Apr
2024

Volume
55

Issue
02

SCRIPTA MEDICA

ISSN 2490-3329 (Print)
ISSN 2303-7954 (Online)

ASSOCIATION OF MEDICAL DOCTORS OF THE REPUBLIC OF SRPSKA,
FACULTY OF MEDICINE, UNIVERSITY OF BANJA LUKA

www.scriptamedica.com

Published by Faculty of Medicine University of Banja Luka

SCRIPTA MEDICA

ASSOCIATION OF MEDICAL DOCTORS OF THE REPUBLIC OF SRPSKA,
FACULTY OF MEDICINE, UNIVERSITY OF BANJA LUKA

BANJA LUKA, March - April 2024

CONTENT

ISSN 2490-3329 (Print) ISSN 2303-7954 (Online)
SCRIPTA MEDICA 2024 | 55 | 02 (Mar-Apr)

EDITORIAL BOARD

Editor-in-Chief
Miloš P Stojiljković,
Banja Luka, RS, B&H

Senior Associate Editor
Ranko Škrbić,
Banja Luka, RS, B&H

Associated Editors
Radoslav B Gajanin
Banja Luka, RS, B&H
Zoran Vujković
Banja Luka, RS, B&H
Nenad Ponorac
Banja Luka, RS, B&H

Junior Editor
Žana M Maksimović
Banja Luka, RS, B&H

Members
Devendra K Agrawal, Pomona, CA, USA
Hani Al-Salami, Perth, WA, Australia
Istvàn Baczkò, Szeged, Hungary
Jacob Bergsland, Oslo, Norway
Miodrag J Čolić, Belgrade, Serbia
Samir Delibegović, Tuzla, FBH, B&H
Naranjan S Dhalla, Winnipeg, MB, Canada
Mirza Dilić, Sarajevo, FBH, B&H
Dragan M Djuric, Belgrade, Serbia
Brent M Egan, Greenville, SC, USA
M Faadiel Essop, Cape Town, South Africa
Heno Ferreira Lopes, Sao Paulo, Brazil
Nirman K Ganguli, New Delhi, India
Ramesh K Goyal, New Delhi, India
Ognjen Gajic, Rochester, MN, USA
Darko Golić, Banja Luka, RS, B&H
Vojka Gorjup, Ljubljana, Slovenia
Hossein Hassanian-Moghaddam, Tehran, Iran
Guo-Wei He, Tianjin, China
Rajko Igić, Chicago, IL, USA
Rowland O Illing, London, England, UK
Slavenka Janković, Belgrade, Serbia
Jasmin Komić, Banja Luka, RS, B&H
Tamara Kovačević-Preradović, Banja Luka, RS, B&H
Zdenka Krivokuća, Banja Luka, RS, B&H
Kamil Kuča, Hradec Kralove, Czechia
Nebojša M Lalić, Belgrade, Serbia
Stephen M Lanier, Detroit, MI, USA
Dragana Lončar-Stojiljković, Belgrade, Serbia
Vanda Marković-Peković, Banja Luka, RS, B&H
Amela Matavulj, Banja Luka, RS, B&H
Milka Mavija, Banja Luka, RS, B&H
Lana Nežić, Banja Luka, RS, B&H
Milomir Ninković, Munich, Germany
Miodrag Č Ostojić, Belgrade, Serbia
Philip M P Poortmans, Antwerp, Belgium
Rade D Paravina, Houston, TX, USA
Verica Pavlić, Banja Luka, RS, B&H
Miroslav R Petković, Banja Luka, RS, B&H
Predrag Peško, Belgrade, Serbia
Jelica Predojević-Samardžić, Banja Luka, RS, B&H
Nela Rašeta Simović, Banja Luka, RS, B&H
Ricky A Sharma, London, England, UK
Wataru Shimizu, Tokyo, Japan
Milan Simatović, Banja Luka, RS, B&H
Tatjana Simić, Belgrade, Serbia
Osman Sinanović, Tuzla, FBH, B&H
Petar Slankamenac, Novi Sad, Serbia
Ranbir C Sobti, Chandigarh, India
Svjetlana Stoisavljević-Šatara, Banja Luka, RS, B&H
George R Sutherland, London, England, UK
Nebojša M Tasić, Belgrade, Serbia
Gordana Tešanović, Banja Luka, RS, B&H
Tibor Tot, Falun, Sweden
Belma Turan, Ankara, Turkey
Antonija Verhaz, Banja Luka, RS, B&H
Stojko Vidović, Banja Luka, RS, B&H
Vlastimir Vlatković, Banja Luka, RS, B&H
Gordan M Vujanić, Doha, Qatar
Duško Vulić, Banja Luka, RS, B&H
Nathan D Wong, Irvine, CA, USA
Enver Zerem, Sarajevo, FBH, B&H
Andreas Zuckermann,Vienna, Austria

Manager
Slavica Serdar Janjuš

Layout and Prepress
Dragan Prlja

Printed by
Grafix s.p., Banjaluka

Publishers
Association of Medical Doctors of the Republic of Srpska,
Faculty of Medicine, University of Banja Luka

PUBLISHING COUNCIL

Co-Presidents
Siniša Miljković
Ranko Škrbić

Members
Tatjana Nožica-Radulović
Goran Spasojević
Radoslav Gajanin
Peđa Kovačević
Dražan Erić
Milenko Krneta

Indexed/Abstracted by
EBSCO, Google Scholar, Crossref, SCIndeks, DOAJ, KoBSON, Index Copernicus International (ICI) - Journals Master List, Dimensions, Sherpa/Romeo, Scopus.

CONTENT

Original Articles

Review Articles

Current Topics

History of Medicine

Professional Article

Sarma et al. Scr Med. 2024 Mar-Apr;55(2):127-36. DOI:10.5937/scriptamed55-46000

ORIGINAL ARTICLE

Radiation Exposure Assessment in Coronary Angiography Computed Tomography Scan: Establishing Diagnostic Reference Level for Northeast Assam Population

Arnabjyoti Deva Sarma,[1] Jibon Sharma,[2] Manash Pratim Sarma,[3] Mrinal Kanti Singha[3]

1. Assam Down Town University, Department of Radiology, Panikhaiti, Guwahati, Assam, India.
2. State Cancer Institute, Gauhati Medical College and Hospital, Guwahati, Assam, India.
3. Assam Down Town University, Department of Biotechnology, Panikhaiti, Guwahati, Assam, India.

Citation:
Sarma AD, Sharma J, Sarma MP, Singha MK. Radiation exposure assessment in coronary angiography computed tomography scan: establishing diagnostic reference level for northeast Assam population. Scr Med. 2024 Mar-Apr;55(2):127-36.

Corresponding author:
ARNABJYOTI DEVA SARMA
E: drarnab1990@yahoo.com
T: +916901607196

Abstract

Background/Aim: Coronary angiography computed tomography (CT) scans play a pivotal role in diagnosing cardiovascular diseases, providing crucial information for treatment planning. However, concerns regarding radiation exposure have prompted the need for establishing region-specific diagnostic reference levels (DRLs) to ensure patient safety. This study aimed to assess radiation exposure during coronary angiography CT scans in the northeast Assam population and establish DRLs tailored to this demographic.

Methods: A total of 380 patients were referred to the Primus Diagnostic Centre and Heath City Hospital, Guwahati Assam with coronary artery disturbances. Data on the technical parameters used in CT procedures were taken in 2021-2022. Organ and surface dose to specific radiosensitive organs (chest) estimation was done using software *imPACT 1.0.4* from the National Radiological Protection Board (NRPB) SR250 Monte Carlo dataset.

Results: The study population (n = 380) comprised 190 men and 190 women with an age range from 29 to 75 years. The mean body mass index (BMI) and effective dose (ED) were 22.42 ± 1.06 kg/m^2 and 21.57 ± 4.27 mSv.cm, respectively. The mean the dose-length product (DLP) was 854.67 mSv.cm and the mean ED was 21.57 mSv.cm. The ED for males was 13-27 mSv and 13-29 mSv for females. The DRL for the male population was found to be 24.26 mSv.cm^2 whereas for the female population was 24.69 mSv.cm^2.

Conclusion: This study highlights the necessity of establishing tailored DRLs for coronary angiography CT scans in the northeast Assam population. By doing so, healthcare providers can ensure optimal image quality while minimising radiation exposure, ultimately enhancing patient safety and quality of care. These findings have implications for radiological practice in the region and contribute to the ongoing efforts to standardise radiation doses in medical imaging procedures.

Key words: Radiology; Computed tomography; Coronary angiography; Phantom; Heart.

Received: 15 August 2023
Revision received: 3 December 2023
Accepted: 3 December 2023

Introduction

In the 1970s, computed tomography (CT) was invented by British engineer Godfrey N Hounsfield and American surgeon AM Cormack by integrating X-ray technology with computers. This innovative X-ray method depicts not only bones but also surrounding tissues by collecting slice-by-

Copyright © 2024 Sarma et al. This is an open access article distributed under the Creative Commons Attribution License (CC BY), which permits unrestricted use, distribution and reproduction in any medium, provided the original work is properly cited.

slice images of various body parts. A few years before, Cormack had developed an approach for determining the distribution and attenuation of X-rays within the body as well as a mathematical theory for image reconstruction. In 1979, the two scientists received the Nobel Prize in Medicine for their efforts and discovery.[1, 2] Understanding the balance between diagnostic benefits and potential radiation risks is crucial for informed decision-making.

Coronary arteries are the "arterial blood vessels" that provide the heart muscle with oxygenated blood *via* coronary circulation. The heart, like all other organs or tissue in the body, needs an ongoing oxygen supply to operate and survive.[3] The coronary arteries encircle the whole heart. The right and left coronary arteries are two main types of coronary arteries that supply blood to the heart. These arteries can also be classified into different groups based on the regions of the heart that they supply with blood flow. These classifications are referred to as microvascular classifications, which supply blood to the innermost heart tissue, or near the endocardium and epicardial classifications, which supply blood across the epicardium, or the outermost heart tissue.[4] A bridged coronary artery function may lead to less blood carrying nutrients and oxygen to the heart. This may have an impact on the heart's capacity to circulate blood throughout the body as well as on the blood supply to the heart muscle itself. Consequently, any disease or illness of the coronary arteries could have a significant health effect and even cause heart attack, angina, or even mortality.[5] The left coronary artery (LCA) and right coronary artery (RCA) which each have multiple branches, make up the majority of the coronary arteries, as illustrated in Figure 1.

Using X-ray technology and computer processing, the medical imaging procedure known as CT angiography may provide precise pictures of the body's blood vessels, including the coronary arteries of the heart. The process utilised in coronary computed tomography angiography (CCTA) or computed tomography angiography (CTA) is specially intended to assess blood flow and obstructions in the coronary arteries. Since there is no need for catheterisation or the insertion of any equipment into the body, the process is non-invasive. Instead, the patient is lying on a table and emits X-rays at various angles. A computer processes the X-ray pictures to produce finely detailed, three-dimensional views of the heart and blood arteries.

The necessity for enhancing blood flow or repairing blocked arteries may need a different technique because there is no catheter insertion performed during a CT coronary angiography (CTCA). The coronary calcium scan is a different method that is comparable to a CTCA. It employs specialised CT images rather than contrast media to evaluate the amounts of calcium or plaque in the constricted arteries. When estimating the risk of main contrary cardiac procedures, a CT angiogram is superior to a coronary CT calcium scan.[6] Although the importance of the low radiation doses utilised in "diagnostic imaging" is uncertain, there is serious concern about the possibility of an increase in cancer incidence

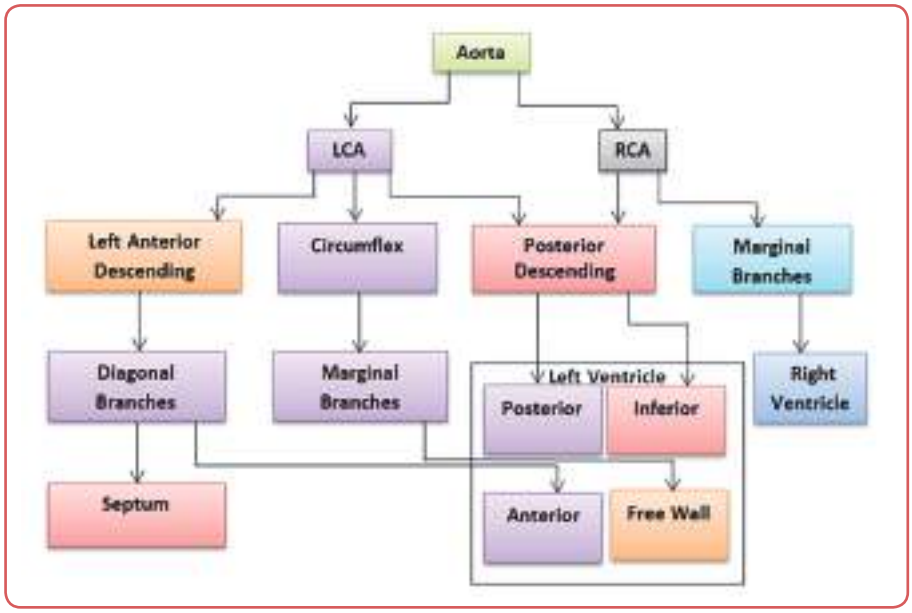


Figure 1: Flow chart depicting the branches of the left and right coronary arteries

CONTENT

in the community. This impending risk must be balanced in contradiction of the risk of failure to identify serious medical issues, such as coronary artery disease, in a particular individual.[7, 8] The diagnostic reference level (DRL) is an essential parameter in medical imaging that helps ensure patients receive the appropriate amount of radiation during procedures such as CTCA.

DRLs is an important dose optimisation tool used in medical imaging recommended by many professional and international organisations, including the International Commission on Radiological Protection (ICRP), the American College of Radiology, the American Association of Physicists in Medicine, the Health Protection Agency and the International Atomic Energy Agency. As a part of the optimisation process and to reduce patient doses in CT examinations, the ICRP introduced DRLs in 1996. As a part of the optimisation process, DRL has been introduced by the ICRP in ICRP publication No 73 in 1996 for common diagnostic procedures and implemented them in a in various regions and countries. DRLs are dose levels determined as 75th percentile of "dose distribution" for X-ray diagnostic investigations, collections of standard phantoms or standard-sized patients for widely different kinds of equipment. In general, when standard procedures are used, it is anticipated that these thresholds will not exceed regular processes. A DRL is never given to a single patient; rather, it is given to a group of individuals. However, comparing a patient's dose to the DRL for a particular examination will give some perspective on whether the dose is reasonable; if it is too high or too low, one must consider the clinical justification for the use of the dose or the image quality, respectively.[9] DRLs are officially described in the ICRP reports as "a type of research level that is applied to an easily measurable quantity, typically the radiation dose absorbed in air or objects that are equivalent to tissue on the surface of a simple standard phantom or a model patient".[10] This explanation highlights that DRLs are not dose limits and do not assist in distinguishing between suitable and improper medical activity. DRLs are different from dose limits, as they can be exceeded if it is clinically necessary to do so. Unlike dose limits for occupational exposure, which only require justification and optimisation, medical exposures are based on clinical judgment. The dose received by a patient during a CT scan can be influenced by factors such as weight and body size. DRLs must not be defined as effective doses (EDs); instead, they should be established as clearly quantifiable and highly reproducible dose metrics for people with standard sizes or phantoms.[11]

Before establishing DRLs, dose measurements are made using a method that has been previously standardised for each kind of radiation examination. Due to the effect of optimisation, DRL may not always apply to current procedures with smaller dose distributions. DRLs developed in specific countries or regions are also frequently assessed to ensure compliance with modifications to standard clinical practice and equipment.

The founding of DRL has provided an enhanced diagnostic advantage across the globe. Data from medical CT procedures must be compared to the reference values to establish DRL. As there are no studies to establish the DRL in Northeast India, it is crucial to establish the standard dose. As recommended by the ICRP in 1991, it is vital to optimise the usage of ionising radiation in healthcare and the current study aimed to compare all the existing data from India and generate baseline information about the existing practice.

This study aimed to assess radiation exposure during CTCA scans in the northeast Assam population and establish DRLs tailored to this demographic.

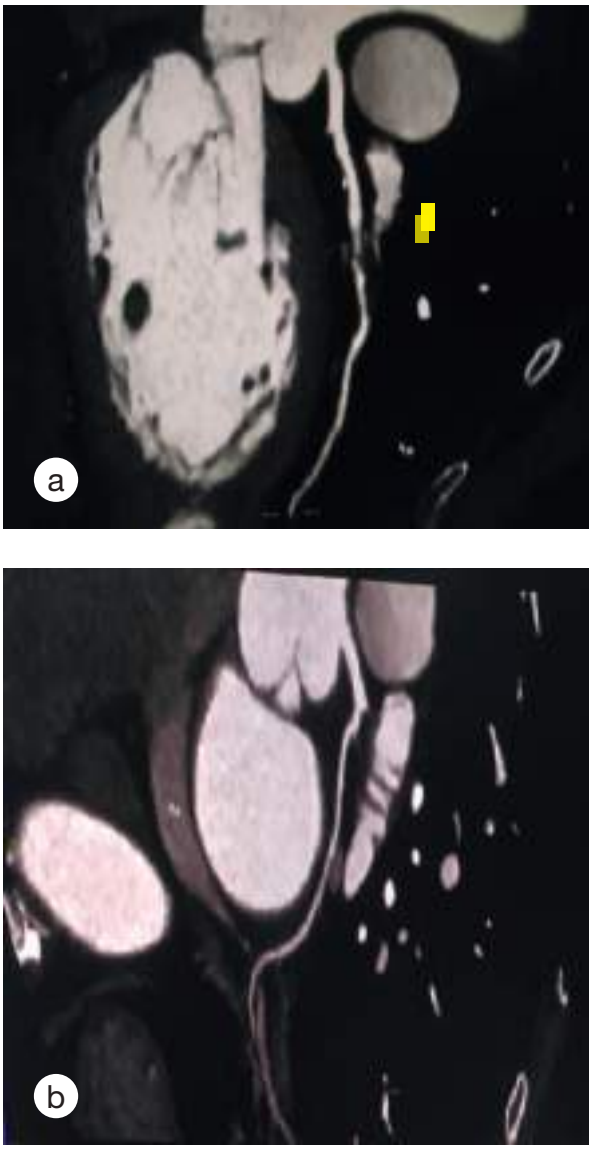
Methods

Dose–response curve as well as the ED received by the patient was analysed. The information used in this research came from one hospital in the Kamrup district of the Assam state (Hospital 1) and one diagnostic centre (Hospital 2). In Hospital 1, CT scan used was *Siemens, Definition AS 12* (128-Slice), Siemens, Munich, Germany. In Hospital 2 a *Philips Ingenuity128* (128-Slice), Philips, Amsterdam, Netherlands scan was used. The study determined a cohort sample size of 380 participants using *Raosoft,* Inc software. This calculation was based on a margin of error of 5 % and a confidence level of 95 %, for a population size of roughly 2,000,000 individuals in Guwahati, Assam. The sample size was determined with consideration of the precision and confidence level desired for the study's results, relative to the estimated population size in the studied area.

CONTENT

For the purpose of this research, data was collected from two different CT scanners. There was one public hospital and one private diagnostic centre having a radiology department that each included the required equipment. In advance of any data collection, the equipment carried out all quality control tests in accordance with the recommendations of Atomic Energy Regulatory Board (AERB). Experiments were carried out by a Radiological Safety officer who had received authorisation from the AERB. Any data tallies that were within a range that was deemed appropriate were included in the study.

To ensure CT scan accuracy, a patient-specific data sheet was used. Every CT machine had a dosimetry CT unit. A data sheet was created to evaluate patient doses and radiation-related factors. Gender, age, tube potential (mA), tube current-time product settings (mAs), pitch, slice thickness and slice count were collected. All scanning parameters, the dose-length product (DLP) in mSv.cm and the CT dose index volume (CTDIvol) were recorded. Each variable affected



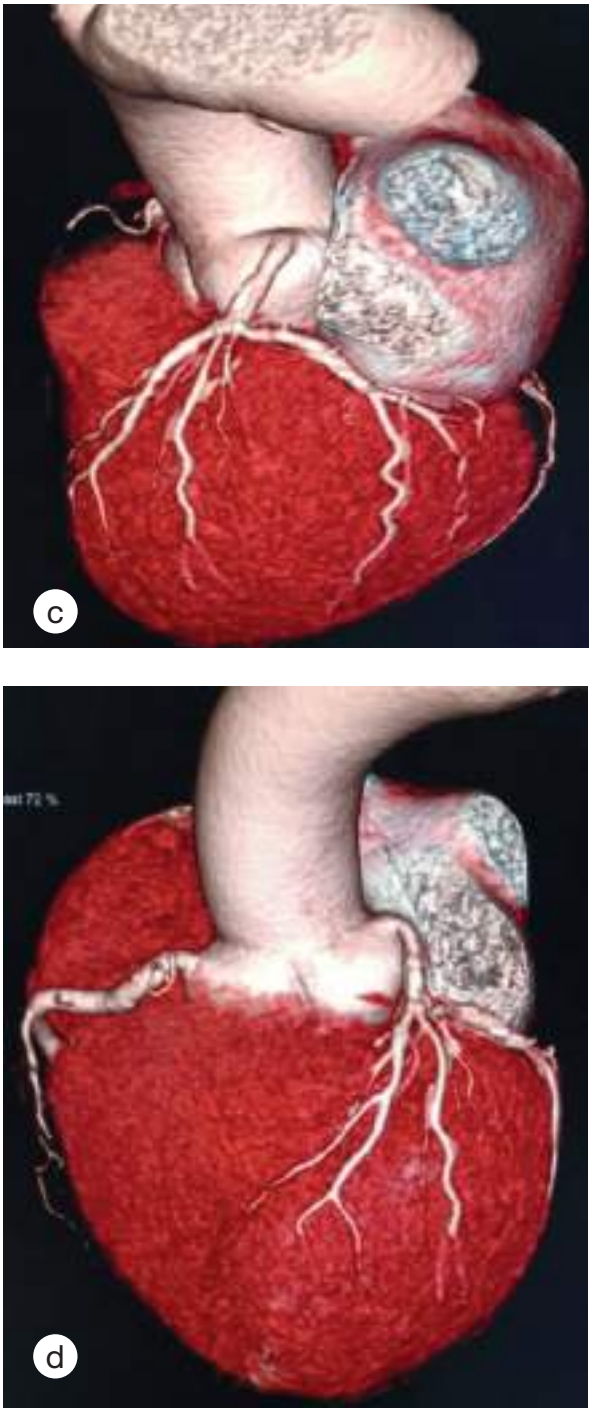


Figure 2: Reconstructed computed tomography - maximum intensity projection (CT-MIP) images (a, b, c, d) illustrating the coronary artery branches

CONTENT

radiation dose differently. The AERB-authorised radiological safety officer had undertaken quality control tests on the hospitals and diagnostic centre's CT equipment and found that they met this research's standards. Ethics were based on ICRP and AERB guidelines (Figures 2-4).

The ImPACT CT patient dosage calculator version 1.0.4, which is a CT dosimetry program that is available for purchase was utilised. In order to compare and validate the dose values that were generated by the CT scanners to evaluate the accuracy of the dose levels generated by the ma-

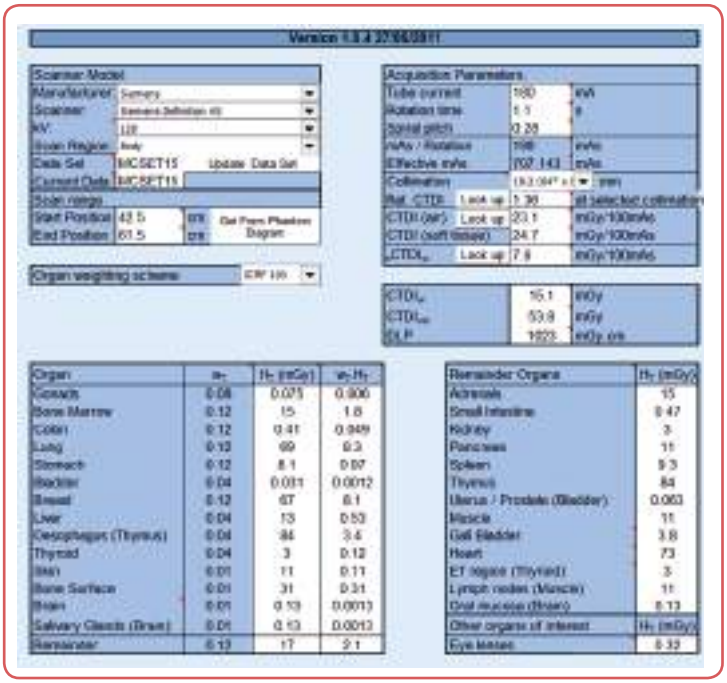


Figure 3: Calculation of effective dose (ED) using imPACT 1.0.4.

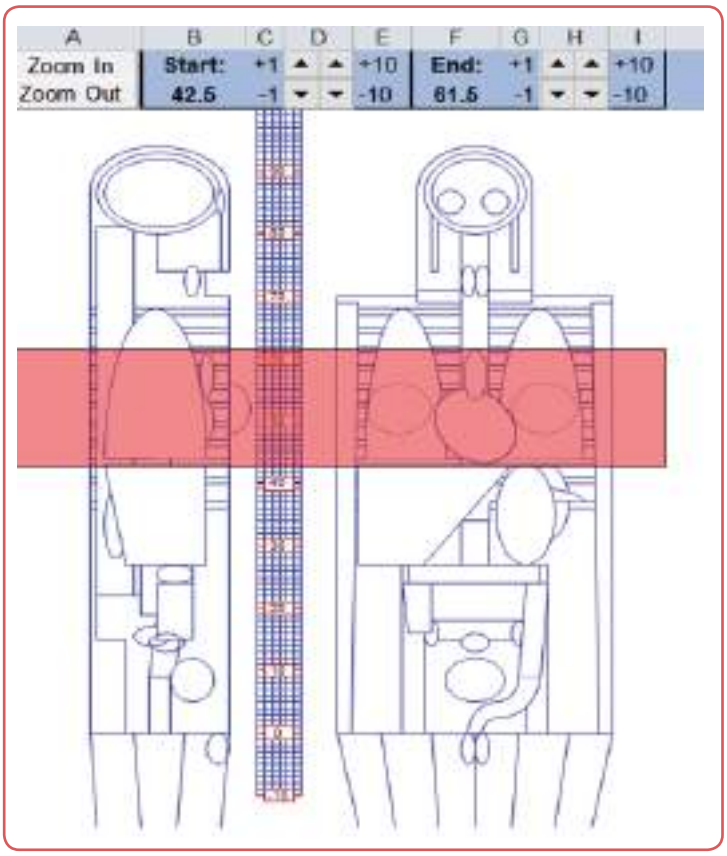


Figure 4: Using a mathematical phantom, effective dose (ED) was calculated. The cardiac scan is shown with a darkened zone between Z = 42.5 and 61.5.

CONTENT

chines. The *imPACT* dose evaluator is a system that uses the SR250 Monte Carlo dataset provided by the National Radiological Protection Board in order to simulate exposure circumstances in mathematical phantoms of many well-known brands of CT scanners.[12] These simulations were performed using the *imPACT* (Figures 2, 3).

Results

In two hospitals, 380 CT scans were measured for radiation exposures for this study. Hospital 1 utilised a *Siemens Definition AS* (128-slice) scanner, whereas Hospital 2 used a *Philips Ingenuity* (128-slice) scanner. The study evaluated DRLs for the two hospitals and gave the dosage measurements in terms of DLP and ED.

Table 1: Patients demographic data for both male and female population

Parameters	Height (m)	Body mass (kg)	Age (years)	BMI (kg/m²)
Range (Max-Min)	1.65-1.57	78-62	75-29	24-19.68
Mean ± SD	1.60 ± 0.02	72.33 ± 4.03	54.67 ± 9.40	22.42 ± 1.05
Median	1.60	72	54	22.42

BMI: body mass index;

Table 1 shows patient demographic data and body mass index (BMI) for both male and female population. The BMI ranged from the minimum weight of 19.68 kg/m² to the maximum weight of 24 kg/m², mean BMI was 22.42 ± 1.05 kg/m².

The statistical analysis of the correlation between BMI and ED for CTCA showed a robust positive correlation between BMI and the radiation received during CTCA (Figure 5). The Pearson r = 0.992 suggested a highly significant linear correlation between BMI and ED, with increasing ED, BMI increases. With an R^2 value of 0.988, the variance accounted for around 98 % of the variance in ED in BMI. This suggests that BMI was a very good predictor of ED for CTCA and that other factors may had little impact on the ED beyond the influence of BMI.

The link between BMI and ED showed a distinct and substantial association between the two factors (Figure 5). Greater BMI levels were shown to correlate to greater EDs, indicating a linear link between the two. The fluctuation in BMI may be used to account for 9.84 % of the variation in the ED, according to the R^2 value of 0.098. A linear connection between BMI (X) and ED (Y) was shown by the equation Y = 1.034X-0.3428.

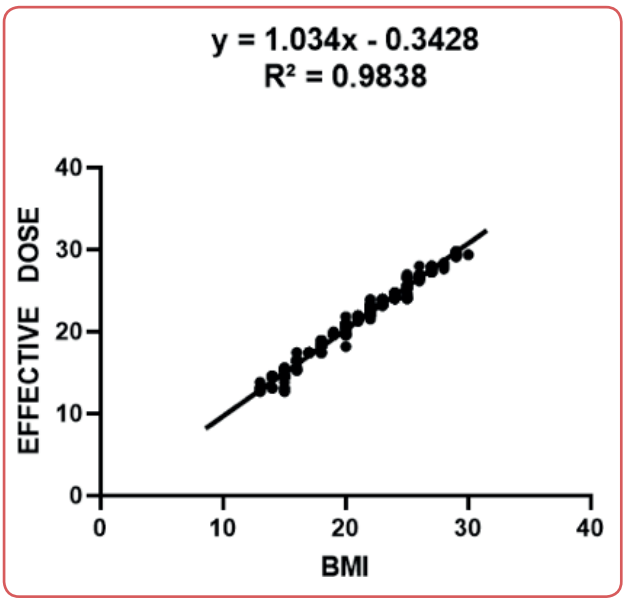


Figure 5: Pearsons correlation of body mass index (BMI) and effective dose (ED)

Table 2: Statistical analysis of effective dose (ED in mSv) for contrast coronary CT angiography related to patients gender

Gender	Dose (mSv)		
	Range (Max-Min)	Mean ± SD	Median
Male	27.99-13.10	21.29 ± 3.80	22.12
Female	29.74-12.73	21.85 ± 4.66	22.99
All patients	29.74-12.73	21.57 ± 4.27	22.12

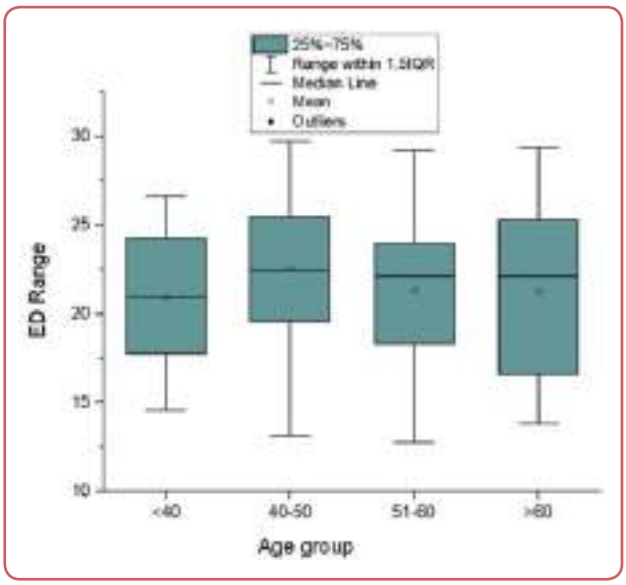


Figure 6: Effective dose (ED) related to age in the studied population

CONTENT

Values of ED related to gender is shown in Table 2. Mean ED were 21.29 ± 3.80, 21.85 ± 4.66 and 21.57 ± 4.27, for males, females and both sexes, respectively. Male patients received a slightly lower radiation dose than female patients during contrast CTCA, however, the difference was insignificant. ED related to age is shown in Figure 6.

Table 3: The diagnostic reference levels (DRL) for the studied population

Population	DRL (mSv.cm^2)
Male	24.26
Female	24.69
All	24.45

The correlation in DRL for CTCA cases across all cases is shown in Table 3. The DRL values were 24.26 mSv.cm^2 for males, 24.69 mSv.cm^2 for females and 24.45 mSv.cm^2 for all patients.

Discussion

The demographic profile of patients undergoing CTCA can provide important information that can aid in the diagnosis, treatment and prevention of cardiovascular diseases.[13] Some important aspects of a patient's demographic profile relevant to CTCA include age, gender, race/ethnicity, medical history and lifestyle factors such as smoking, diet and exercise habits.[14] The mean and median values being close to each other suggest that the distribution of BMI values is roughly symmetric. The relatively small standard deviation of 1.05 kg/m^2 indicates that the BMI values are tightly clustered around the mean. Overall, this information suggests that the population or sample from which the BMI values were obtained has a relatively narrow range of BMI values and is likely to be relatively homogeneous with respect to BMI.
Numerous studies have focused on the relationship between BMI and ED for CTCA. A study discovered a positive correlation between BMI and ED for CTCA, with an average increase of 18 % in ED for every increment of 5 kg/m^2 in BMI.[15] According to another study, the ED for CTCA rose by 13 % with each 5 kg/m^2 increase in BMI.[16] They recommended that for patients undergoing CTCA, radiologists should be aware of the association between BMI and radiation exposure and take steps to minimise the radiation dose whenever possible, such as by using lower tube voltage and current settings, optimising scan parameters and using dose-reduction techniques.

Similar studies have demonstrated that a higher BMI is linked to an increased radiation dosage because adipose tissue absorbs less radiation due to its lower density than other tissues.[17, 18] Another study found that higher BMI was associated with increased radiation exposure during medical imaging, particularly for CT scans. The authors noted that this could have important implications for cancer risk, given the known association between radiation exposure and cancer.[19] The R^2 value of 0.098 suggested that only 9.8 % of the variability in ED can be explained by BMI. While this relationship is statistically significant, it is relatively weak and other factors such as age, sex and the specific imaging procedure being performed may also play a role in determining an ED.

ED is a measure of the amount of radiation energy that is absorbed by the body during a medical imaging test and it considers the type of radiation and the sensitivity of the different organs in the body to radiation. Male patients received a slightly lower radiation dose than female patients during contrast CTCA, which was also reported in other CT studies.[20]

The mean ED ranges for males and females were approximately 13 to 28 mSv and 12 to 29 mSv, respectively. This indicates that there is a wide variability in the amount of radiation exposure that patients receive during this type of imaging test. It is essential to minimise radiation exposure to patients during imaging tests, especially for those who may require multiple tests or who are more sensitive to radiation. This is where radiation dose reduction techniques become important. These techniques involve optimising the imaging parameters, such as the tube current, tube voltage and scan duration, to reduce the radiation exposure while still obtaining high-quality images for accurate diagnosis. It is crucial to note that the ED range shown is influenced by several factors, including patient size, the type of scanner used, the scan protocol and the operator's skill level. Therefore, it is essential to follow standard imaging protocols and to have well-trained operators to minimise the variability in radiation exposure between patients.[21, 22]

It is important to regard age as a potential factor when optimising imaging protocols and reducing radiation doses in patients. It is generally understood that age may have a substantial impact on how much radiation is exposed during medical imaging exams.[23, 24] Older patients may require

CONTENT

higher radiation doses to obtain images of sufficient quality due to factors such as increased body size, higher BMI and the presence of medical comorbidities. It is vital to note that radiation exposure from medical imaging tests, including contrast CTCA, can pose potential risks to patients, especially those who are more vulnerable, such as children and pregnant women.[19, 25] Therefore, it is crucial to use the as low as reasonably achievable (ALARA) principle to reduce radiation exposure in patients while preserving diagnostic image quality.[26, 27]

The use of the phantom to quantify CT dosage was the study's principal flaw. Since it considers both controllable (imaging technique, tube voltage, tube current) and uncontrollable (patient orientation, collimation and distance) factors, the use of the patients may have been preferable. Even though using phantom produces almost identical exposures, it only addresses elements under our control.[28]

DRLs are recommended levels of radiation exposure for typical patients undergoing a specific type of imaging procedure.[29] They are meant to be a benchmark to optimise imaging protocols and reduce unnecessary radiation exposure while maintaining image quality.[30] It should be emphasised that these values do not represent absolute limits and certain patients may require higher doses for diagnostic purposes based on factors such as their age, body size and the specific medical condition being examined. Nevertheless, medical practitioners should carefully evaluate the potential risks and benefits of the imaging procedure and aim to use the lowest possible dose that will still provide the necessary diagnostic information. Individuals with a low pre-test probability of CAD, such as women with a narrow anteroposterior chest diameter, anxiety and mitral valve prolapse, who are commonly diagnosed with false positive exercise or echocardiology stress test, should not undergo CTCA. Another category for which CTCA could be avoided is represented by elderly males with increased cardiovascular disease burden and high pre-test probability of CAD. The latter should directly undergo coronary angiography especially if they are symptomatic.[31]

Conclusion

The current study findings pertaining to the population heterogeneity to DRLs level may be helpful for diagnosis purposes in this part of the country. Also, the reduction in the dose in exposure purpose by the present study may be taken into consideration in reduced exposure at the same time without compromising the images. It is advised that the current study contributes to the establishment of scanning parameters with regard to the patient's size and the body region of interest being scanned.

Ethics

Study was approved by the Assam Down Town University Ethical Committee, decision No AdtU/Ethics/PhD Scholar/2021/009, dated 24 September 2021.

Acknowledgement

Authors acknowledge Assam Downtown University for allowing us to conduct this study.

Conflicts of interest

The authors declare that there is no conflict of interest.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Data access

The data that support the findings of this study are available from the corresponding author upon reasonable individual request.

Author ORCID numbers

Arnabjyoti Deva Sarma (ADS):
0000-0003-2505-2790
Jibon Sharma (JS):
0000-0003-3944-2159
Manash Pratim Sarma (MPS):
0009-0006-1282-9643
Mrinal Kanti Singha (MKS):
0000-0002-3709-7251

Author contributions

Conceptualisation: ADS, MPS, JS
Methodology: JS, ADS
Software: JS
Validation: MPS
Formal analysis: MPS
Investigation: ADS
Resources: ADS, MPS
Data curation: ADS, JS
Writing - original draft: ADS, MPS
Writing - review and editing: ADS
Visualisation: JS, MPS
Supervision: ADS, MPS, JS
Project administration: ADS
Funding acquisition: JS.

References

1. Kalender WA. Dose in X-ray computed tomography. Phys Med Biol. 2014 Feb 7;59(3):R129-50. doi: 10.1088/0031-9155/59/3/R129.
2. Hsieh, J. Computed tomography: principles, design, artifacts, and recent advances. Bellingham, WA: SPIE; 2003.
3. Fernandes ED, Kadivar H, Hallman GL, Reul GJ, Ott DA, Cooley DA. Congenital malformations of the coronary arteries: the Texas Heart Institute experience. Ann Thorac Surg. 1992 Oct;54(4):732-40. doi: 10.1016/0003-4975(92)91019-6.
4. Petersen JW, Pepine CJ. Microvascular coronary dysfunction and ischemic heart disease: where are we in 2014? Trends Cardiovasc Med. 2015 Feb;25(2):98-103. doi: 10.1016/j.tcm.2014.09.013.
5. Douglas PS, Hoffmann U, Patel MR, Mark DB, Al-Khalidi HR, Cavanaugh B, et al; PROMISE Investigators. Outcomes of anatomical versus functional testing for coronary artery disease. N Engl J Med. 2015 Apr 2;372(14):1291-300. doi: 10.1056/NEJMoa1415516.
6. Hou ZH, Lu B, Gao Y, Jiang SL, Wang Y, Li W, et al. Prognostic value of coronary CT angiography and calcium score for major adverse cardiac events in outpatients. JACC Cardiovasc Imaging. 2012 Oct;5(10):990-9. doi: 10.1016/j.jcmg.2012.06.006.
7. Hart D, Wall BF. Radiation exposure of the UK population from medical and dental X-ray examinations. Chilton, UK: NRPB; 2002. doi: 10.1016/s0720-048x(03)00178-5.
8. Gerber TC, Carr JJ, Arai AE, Dixon RL, Ferrari VA, Gomes AS, et al. Ionizing radiation in cardiac imaging: a science advisory from the American Heart Association Committee on Cardiac Imaging of the Council on Clinical Cardiology and Committee on Cardiovascular Imaging and Intervention of the Council on Cardiovascular Radiology and Intervention. Circulation. 2009 Feb 24;119(7):1056-65. doi: 10.1161/circulationaha.108.191650.
9. Abdullah, A. Establishing dose reference level for computed tomography (CT) examinations in Malaysia. Gelugor, Malaysia: Universiti Sains Malaysia, 2009.
10. The 2007 Recommendations of the International Commission on Radiological Protection. ICRP publication 103. Ann ICRP. 2007;37(2-4):1-332. doi: 10.1016/j.icrp.2007.10.003.
11. Vassileva J, Rehani M. Diagnostic reference levels. AJR Am J Roentgenol. 2015 Jan;204(1):W1-3. doi: 10.2214/AJR.14.12794.
12. Sarma AD, Singha M.K, Sharma J. Estimation of patients effective dose with respect to BMI using Monte Carlo simulation method for CT coronary angiography patients. NeuroQuantology. 2022;20(22):549-9. doi: 10.48047/nq.2022.20.22.NQ10043.
13. Aupongkaroon P, Makarawate P, Chaosuwannakit N. Comparison of radiation dose and its correlates between coronary computed tomography angiography and invasive coronary angiography in Northeastern Thailand. Egypt Heart J. 2022 Jan 25;74(1):6. doi: 10.1186/s43044-022-00241-5.
14. Kones R. Recent advances in the management of chronic stable angina I: approach to the patient, diagnosis, pathophysiology, risk stratification, and gender disparities. Vasc Health Risk Manag. 2010 Aug 9;6:635-56. doi: 10.2147/vhrm.s7564.
15. Einstein AJ, Henzlova MJ, Rajagopalan S. Estimating risk of cancer associated with radiation exposure from 64-slice computed tomography coronary angiography. JAMA. 2007 Jul 18;298(3):317-23. doi: 10.1001/jama.298.3.317.
16. Hausleiter J, Meyer T, Hermann F, Hadamitzky M, Krebs M, Gerber TC, et al. Estimated radiation dose associated with cardiac CT angiography. JAMA. 2009 Feb 4;301(5):500-7. doi: 10.1001/jama.2009.54.
17. Shah A, Das P, Subkovas E, Buch AN, Rees M, Bellamy C. Radiation dose during coronary angiogram: relation to body mass index. Heart Lung Circ. 2015 Jan;24(1):21-5. doi: 10.1016/j.hlc.2014.05.018.
18. Wang R, Schoepf UJ, Wu R, Reddy RP, Zhang C, Yu W,

CONTENT

et al. Image quality and radiation dose of low dose coronary CT angiography in obese patients: sinogram affirmed iterative reconstruction versus filtered back projection. Eur J Radiol. 2012 Nov;81(11):3141-5. doi: 10.1016/j.ejrad.2012.04.012.
19. Lin EC. Radiation risk from medical imaging. Mayo Clin Proc. 2010 Dec;85(12):1142-6; quiz 1146. doi: 10.4065/mcp.2010.0260.
20. Hunold P, Vogt FM, Schmermund A, Debatin JF, Kerkhoff G, Budde T, et al. Radiation exposure during cardiac CT: effective doses at multi-detector row CT and electron-beam CT. Radiology. 2003 Jan;226(1):145-52. doi: 10.1148/radiol.2261011365.
21. McCollough CH, Primak AN, Braun N, Kofler J, Yu L, Christner J. Strategies for reducing radiation dose in CT. Radiol Clin North Am. 2009 Jan;47(1):27-40. doi: 10.1016/j.rcl.2008.10.006.
22. Gottumukkala RV, Kalra MK, Tabari A, Otrakji A, Gee MS. Advanced CT techniques for decreasing radiation dose, reducing sedation requirements, and optimizing image quality in children. Radiographics. 2019 May-Jun;39(3):709-26. doi: 10.1148/rg.2019180082.
23. Alzen G, Benz-Bohm G. Radiation protection in pediatric radiology. Dtsch Arztebl Int. 2011 Jun;108(24):407-14. doi: 10.3238/arztebl.2011.0407.
24. Smith-Bindman R, Miglioretti DL, Johnson E, Lee C, Feigelson HS, Flynn M, et al. Use of diagnostic imaging studies and associated radiation exposure for patients enrolled in large integrated health care systems, 1996-2010. JAMA. 2012 Jun 13;307(22):2400-9. doi: 10.1001/jama.2012.5960.
25. Power SP, Moloney F, Twomey M, James K, O'Connor OJ, Maher MM. Computed tomography and patient risk: Facts, perceptions and uncertainties. World J Radiol. 2016 Dec 28;8(12):902-15. doi: 10.4329/wjr.v8.i12.902.
26. Hausleiter J, Meyer T. Tips to minimize radiation exposure. J Cardiovasc Comput Tomogr. 2008 Sep-Oct;2(5):325-7. doi: 10.1016/j.jcct.2008.08.012.
27. Shah NB, Platt SL. ALARA: is there a cause for alarm? Reducing radiation risks from computed tomography scanning in children. Curr Opin Pediatr. 2008 Jun;20(3):243-7. doi: 10.1097/MOP.0b013e3282ffafd2.
28. Sarma AD, Singha MK, Sharma J, Kashyap DMP. Estimation of effective dose in Monte Carlo simulation method for CT coronary angiography patients. Int J Life Sci Pharma Res. 2023;13(2):L194–L201. doi: 10.22376/ijlpr.2023.13.2.L194-L201.
29. Thomas P. National diagnostic reference levels: What they are, why we need them and what's next. J Med Imaging Radiat Oncol. 2022 Mar;66(2):208-14. doi: 10.1111/1754-9485.13375.
30. Wall BF. Diagnostic reference levels--the way forward. Br J Radiol 2001 Sep;74(885):785-8. doi: 10.1259/bjr.74.885.740785.
31. Sonaglioni A, Rigamonti E, Nicolosi GL, Lombardo M. Appropriate use criteria implementation with modified Haller index for predicting stress echocardiographic results and outcome in a population of patients with suspected coronary artery disease. Int J Cardiovasc Imaging. 2021 Oct;37(10):2917-30. doi: 10.1007/s10554-021-02274-4.

CONTENT

Joshi et al. Scr Med. 2024 Mar-Apr;55(2):137-48. DOI:10.5937/scriptamed55-47571

ORIGINAL ARTICLE

Unveiling the Spatial Pattern and Determinants of Child Anaemia in India - National Family Health Survey-5 Chronicles (NFHS-5)

Abhijeet Joshi,[1] Deepak Tanwar,[2] Pawan Kumar Dubey,[3] Mukesh Vishwakarma,[4] Sabrina Sultana Rahman[5]

Abstract

Background/Aim: Childhood anaemia continues to persist as a prominent nutritional disease and a public health challenge in India despite several initiatives by the Government of India. This study aimed to identify predictors and regional disparities for targeted interventions.

Methods: This study utilised data from a nationally representative cross-sectional survey from the fifth round of the National Family Health Survey (NFHS-5), encompassing 177,695 children aged 6-59 months across 707 districts and 36 states and union territories of India. It employed multivariate logistic regression and spatial analysis at district levels to examine socio-demographic predictors and spatial patterns of childhood anaemia in the country.

Result: Multivariate logistic results revealed, women aged 15–19 were 2.43 times more likely to have an anaemic child compared to those aged 35–49 and uneducated mothers had a 29 % higher likelihood of having an anaemic child. There was positive spatial autocorrelation (Moran's I value = 0.579) at the district level in India, with 108 identified hotspots in regions including Jammu and Kashmir, Ladakh, Gujarat, Maharashtra, Telangana, Uttar Pradesh, Rajasthan, Jharkhand, Chhattisgarh and Bihar. The spatial error model (SEM) indicated that mother's anaemia (0.53) and maternal education (0.23) were key predictors of child anaemia in India.

Conclusion: The study findings provide valuable understanding regarding the socio-demographic predictors associated with childhood anaemia such as adolescent motherhood, low education, lack of media exposure, higher birth order and rural residence. Also, the spatial study provides the spatial heterogeneity of childhood anaemia at the district level and advocates more attention toward hotspot regions in the country.

Key words: Childhood anaemia; Logistic regression; LISA; Spatial error model.

1. Department of Anatomy, Government Medical College, Barmer, Rajasthan, India.
2. Department of Community Medicine, Government Medical College, Barmer, Rajasthan, India.
3. Monitoring and Evaluation, India Health Action Trust, Lucknow, Uttar Pradesh, India.
4. Department of Mathematics and Statistics, Banasthali Vidyapith, Rajasthan, India.
5. Department of Statistics, Cotton University, Assam, India.

Citation:
Joshi A, Tanwar D, Dubey PK, Vishwakarma M, Rahman SS. Unveiling the spatial pattern and determinants of child anaemia in India - National Family Health Survey-5 chronicles (NFHS-5). Scr Med. 2024 Mar-Apr;55(2):137-48.

Corresponding author:
MUKESH VISHWAKARMA
E: vishwakarma.m96@gmail.com

Received: 6 November 2023
Revision received: 7 March 2024
Accepted: 7 March 2024

Introduction

Anaemia among children continues to be a serious public health issue in low- and middle-income nations. The poor world is still battling with catastrophic issues like poverty, starvation and malnutrition in the modern-era world, where rich nations are moving toward new technologies and successes. Due to socioeconomic developments and the emergence of international

Copyright © 2024 Joshi et al. This is an open access article distributed under the Creative Commons Attribution License (CC BY), which permits unrestricted use, distribution and reproduction in any medium, provided the original work is properly cited.

CONTENT

market systems, they are more susceptible to anaemia as they go through a transitional period.[1, 2] The definition of anaemia by World Health Organization (WHO) is: "Anaemia is defined as a haemoglobin concentration below a specified cut-off point; that cut-off point depends on the age, gender, physiological status, smoking habits and altitude at which the population being assessed lives." Anaemia among children under 5 years is defined as the threshold haemoglobin level less than 11.0 g/d·.[3] Iron deficiency, linked to low nutritional iron consumption is one of the critical causes of childhood anaemia in India.[4] Other risk factors equally associated with childhood anaemia include vitamin deficiencies, especially folate, vitamin B_{12} and A, infections with malaria parasite, hookworm and haemoglobinopathies.[5-7] In India the prevalence of anaemia among children aged 6-59 months (haemoglobin levels ≤ 11.0 g/dL) increased dramatically from 59 % National Family Health Survey-4 (NFHS-4) to 67 % (2019–21, NFHS–5).[8] Additionally, with significant regional variation, India is reported to have greatest frequency of anaemia among developing nations.[9] In the absence of timely interceding, these children grow up anaemic and frequently marry beforehand, giving birth to babies with lower iron reserves who turn anaemic within the first months after birth.[10] Hence, there's a need to intermediate in this intergenerational anaemia to insure good health of the overall population.[11-13] Despite India's numerous programs, like POSHAN Abhiyaan and the National Iron Plus Initiative for Anaemia Control, the rate of reduction of child anaemia is not up to the mark and in fact, it has been observed to increase in recent years.[1]

Spatial heterogeneity is a type of seen or unobserved heterogeneity that varies throughout a vast territory or landscape provided by social structure. Spatial heterogeneity (sometimes called sub-regional variation) is the uneven distribution of a trait, event or indication over a region. India has several diverse districts in socioeconomic and demographic statistics. The spatial variance of anaemia cases in Indian districts is little understood.[14] Due to its high sample size, the NFHS-5 provided estimates for a number of crucial anaemia indicators in children. These estimates help to identify district differences and the implementation of customised programs.

The aim of this study was to assess socio-demographic predictors of childhood anaemia in India. Regional heterogeneity and anaemia correlations in Indian districts were also examined.

Methods

The study utilised data from the fifth wave of the National Family Health Survey (NFHS-5), conducted in 2019-21 in India. This nationally representative cross-sectional survey, overseen by the Ministry of Health and Family Welfare, covered all 28 states, 8 union territories and 707 districts. The survey focused on child health and employed a two-stage stratified sampling design. After excluding children with missing data, the final analytic sample comprised 177,695 children aged 6-59 months across all districts and states.

The study's outcome variable was child anaemia prevalence. Explanatory variables, determined through in-depth literature review, encompassed mother's age, residence, education, media exposure, wealth quintile, mother's anaemia, birth order, child's sex, religion and caste.

The study employed multivariate logistic regression to analyse socioeconomic disparities in child anaemia in India. Spatial patterns and clustering of child anaemia were assessed using Moran's I, univariate local indicator of spatial association (LISA), bivariate LISA and a LISA cluster map. The spatial weight matrix (w) of order 1 has been generated using the Queen's contiguity method to quantify the spatial proximity between each possible pair of observational entities in the dataset.[15, 16] Positive spatial autocorrelation suggests that points with comparable attribute values are tightly distributed in space, whereas negative autocorrelation shows that closely associated points are more distinct. Moran's I values range from -1 to +1, with positive and negative values indicating clustering of similar and dissimilar values, respectively. A zero value indicated a random spatial pattern with no spatial autocorrelation. Univariate LISA measured the correlation of neighbourhood values around a specific spatial location. It determined the extent of spatial randomness and clustering present in the data.[17-19]

Four types of spatial autocorrelation were generated:

1. **Hot spots:** High-value areas with similar neighbours (High-High).
2. **Cold spots:** Low values area, with similar neighbours (Low-Low).
3. **Spatial outliers:** High-value areas with low-value neighbours (High-Low).
4. **Spatial outliers:** Low values area with higher values neighbours (Low-High).

CONTENT

To see the potential regional correlates of child anaemia spatial regression analysis which includes ordinary least square (OLS) model and spatial error model (SEM) was performed.[20] Non-spatial analysis was conducted using the trial version of Statistical Package for Social Sciences (SPSS) software v. 26; (IBM Inc, Chicago, IL), while spatial analysis was carried out using trial versions of ArcGIS 10.7 and GeoDa 1.20.

Results

Nearly 90 % out of 177,695 children had mothers aged 20–34 (Table 1). Rural youngsters made up nearly three-quarters of participants. Around half of the women completed their secondary level of education. Anaemia affected 59.8 % of women who gave birth in the five years prior to the survey. Nearly half of the children were of second or third birth order. About one-third of women belonged to schedule caste/ schedule tribe (SC/ ST). Nearly half (46.5 %) of the women were below middle-class category. Media access were unavailable to 28 % of mothers.

In comparison to mothers who were anaemic, mothers without anaemia were 40 % less likely to have an anaemic child (odds ratio (OR): 0.601; 95 % confidence interval (CI): 0.589–0.614). Child anaemia exhibited significant associations with the age of mothers, particularly among younger age groups. For instance, women aged 15–19 years and 20–34 years were 2.431 times (OR: 2.431; 95 % CI: 2.219–2.665) and 1.357 times (OR: 1.357; 95 % CI: 1.29–1.41) more likely to have an anaemic child, respectively, compared to women aged 35–49 years. Furthermore, the education level of mothers emerged as a significant predictor of child anaemia, with higher maternal education associated with reduced odds of child

Table 1: Prevalence of child anaemia with various background characteristics in India (NFHS-5, 2019-21)

Variables	Variable's categories	Weighted frequency (%)	Logistic regression model	
			OR	95 % CI
Age group	15-19	3,580 (2.0)	2.431*	[2.219-2.665]
	20-34	158,870 (89.4)	1.357*	[1.306-1.410]
	35-49	15,246 (8.6)	Ref.	-
Place of residence	Urban	46,559 (26.2)	0.965*	[0.940-0.991]
	Rural	131,136 (73.8)	Ref.	-
Education level of mother	No education	38,010 (21.4)	1.291*	[1.239-1.346]
	Primary	22,094 (12.4)	1.192*	[1.143-1.244]
	Secondary	90,868 (51.1)	1.129*	[1.095-1.164]
	Higher	26,724 (15.0)	Ref.	-
Media exposure	No	50,694 (28.5)	1.082*	[1.053-1.112]
	Yes	127,002 (71.5)	Ref.	-
Wealth index	Poorest	43,640 (24.6)	1.072*	[1.026-1.120]
	Poorer	38,869 (21.9)	1.050*	[1.010-1.093]
	Middle	35,128 (19.8)	1.034	[0.996-1.073]
	Richer	32,850 (18.5)	0.986	[0.952-1.021]
	Richest	27,208 (15.3)	Ref.	-
Anaemia in mother	No	71,482 (40.2)	0.601*	[0.589-0.614]
	Yes	106,213 (59.8)	Ref.	-
Birth order	1st	68,691 (38.7)	0.732*	[0.677-0.792]
	2nd or 3rd	87,878 (49.5)	0.802*	[0.743-0.866]
	4th or 5th	17,046 (9.6)	0.878*	[0.811-0.950]
	≥ 6th	4,081 (2.3)	Ref.	-
Sex of child	Male	92,219 (51.9)	1.003	[0.983-1.023]
	Female	85,476 (48.1)	Ref.	-
Religion	Hindu	141,852 (79.8)	1.268*	[1.207-1.332]
	Muslim	28,082 (15.8)	1.258*	[1.190-1.33]
	Others	7,761 (4.4)	Ref.	-
Caste	Schedule caste	41,491 (23.3)	1.106*	[1.071-1.142]
	Schedule tribe	18,042 (10.2)	1.251*	[1.199-1.305]
	OBC	77,001 (43.3)	0.952*	[0.927-0.978]
	Other	41,161 (23.2)	Ref.	-

**: $p < 0.05$; OR: odds ratio; CI: confidence interval; OBC: other backward class;*

CONTENT

anaemia in India. Specifically, women without any formal education and those with only primary education were 29 % and 19 % more likely to have an anaemic child, respectively, compared to women with higher education.

First-birth order children were 27 % less likely to be anaemic (OR: 0.732; 95 % CI: 0.677–0.792) compared to a child having six or above birth order. Religion also displayed an association with child anaemia, with Hindu and Muslim women being 27 % and 26 % more likely to have anaemic children, respectively, compared to women of other religions. Additionally, children belonging to the scheduled caste (SC) and scheduled tribe (ST) categories were 1.106 times and 1.251 times more likely to have an anaemic child, respectively, when compared to children from other caste groups, excluding SC, ST and other backward class (OBC) categories. No exposure to any kind of media emerged as significant risk factor for child anaemia as women without media exposure were 1.081 times more likely to have anaemic children (OR: 1.082; 95 % CI: 1.053–1.112) compared to their counterparts. Lastly, women from the poorest wealth quintile were 1.072 times more likely to have anaemic children (OR: 1.06; 95 % CI: 1.01–1.12) compared to women from the richest wealth quintile. However, other wealth quintile categories of women, such as those classified as middle and richer, did not exhibit statistically significant differences compared to women in the richest wealth quintile.

Figure 2 represents a LISA scatter plot along with the corresponding Moran's I value (0.579), univariate cluster map and significance map of child anaemia (6-59 months) in the districts of India showing overall clustering of similar behaving districts ie, either high-high or low-low. Out of the 707 districts in India, 108 were identified as hotspots. These hotspots included districts in Jammu Kashmir, Ladakh, Gujarat, Maharashtra, Telangana and several districts in Uttar Pradesh, Rajasthan, Jharkhand and Bihar. Additionally, almost 84 districts were identified as cold spots, indicating that these districts had a low prevalence of child anaemia and were surrounded by districts with similarly low prevalence. These cold spot districts encompassed the entire southern

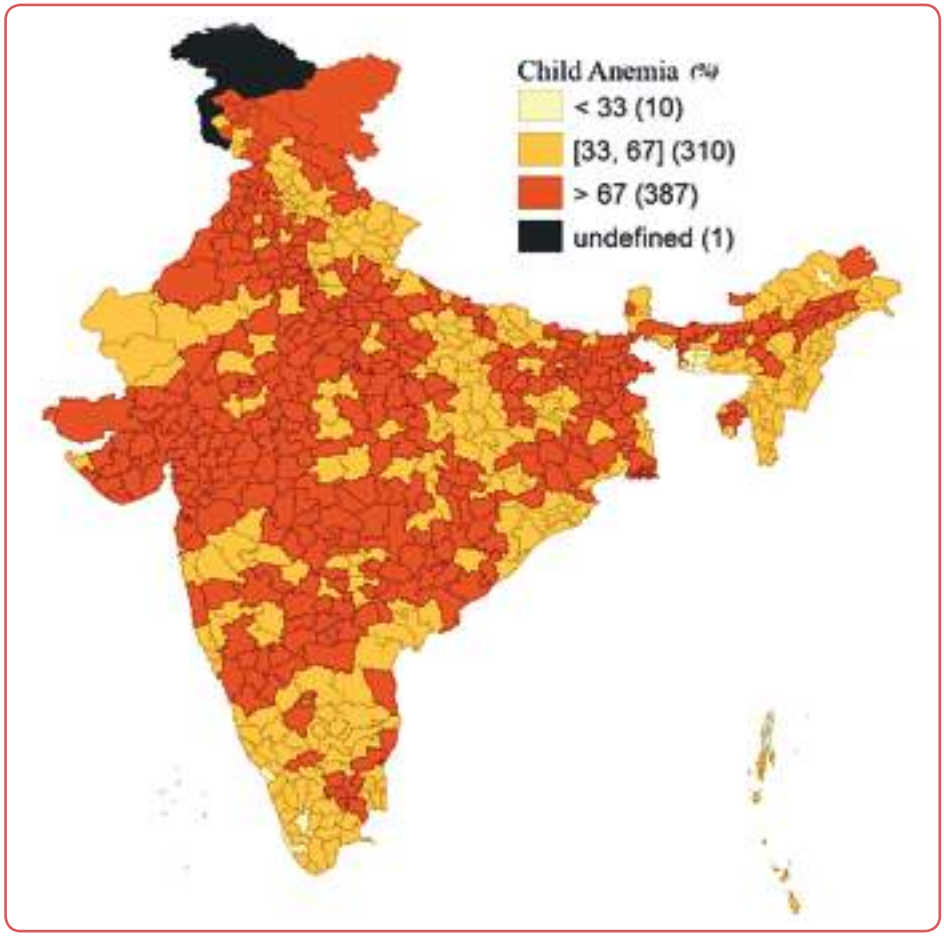


Figure 1: Spatial distribution of prevelance of child anaemia in the districts of India, NFHS-5 (2019-21)

CONTENT

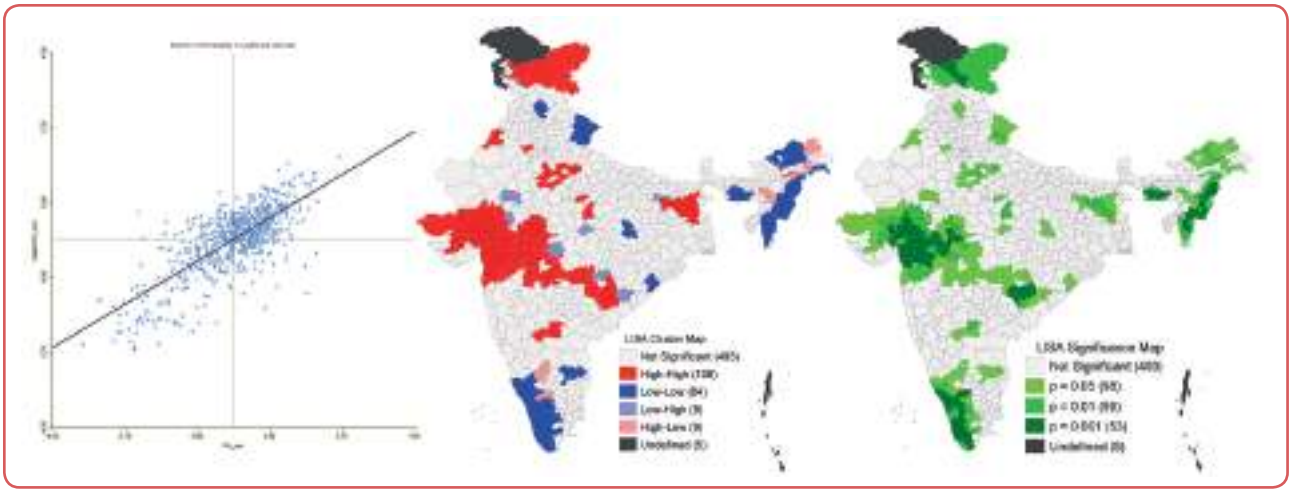


Figure 2: Univariate cluster and local indicator of spatial association (LISA) map showing spatial correlation of child anaemia in the districts level of India, NFHS-5, (2019-21)

LISA cluster map: light grey: not significant (493); dark red: high-high (108); dark blue: low-low (84); light blue: low-high (9); light red: high-low (9); dark grey: undefined (5);

LISA significance map: light grey: not significant (493); light green: p = 0.05 (98); green: p = 0.01 (59); dark green: p = 0.001 (53); dark grey: undefined (5);

and north-eastern parts of India, including Kerala, Tamil Nadu, Karnataka, Arunachal Pradesh, Meghalaya, Nagaland, Mizoram, Manipur, as well as Himachal Pradesh and Uttarakhand in northern India.

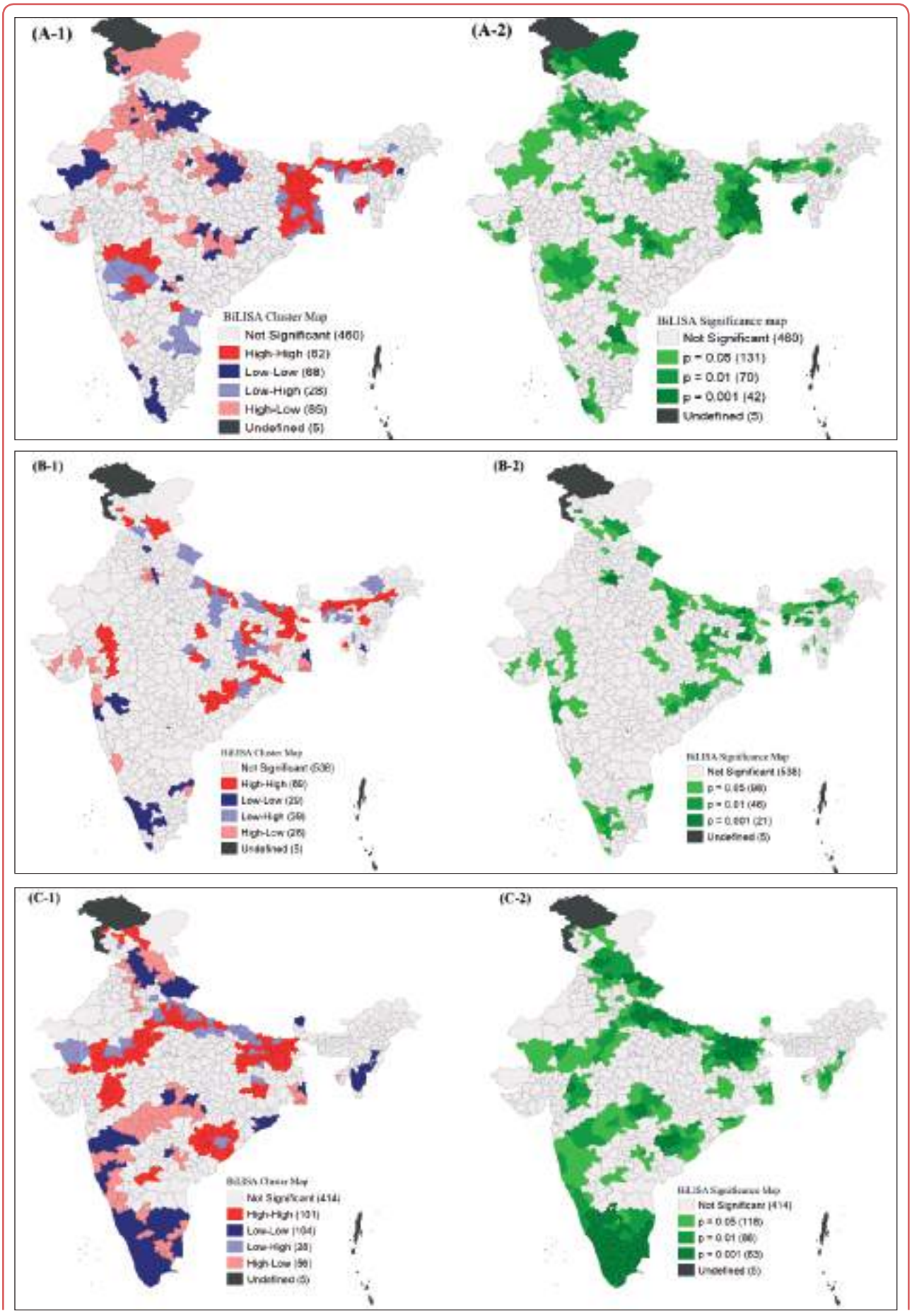
Figure 3 depicts the bivariate LISA map and its corresponding significance map, illustrating the prevalence of child anaemia based on various independent variables in India. Approximately 62 out of the 707 districts exhibited hotspots for child anaemia associated with mothers aged 15–19. These hotspots encompassed states such as Bihar, Jharkhand, West Bengal, Assam, Tripura and certain regions of Maharashtra (map A-1). Among various hotspots and cold spots, 42 districts were coming out to be highly significant (p = 0.001). These districts were mostly concentrated in the Jammu and Kashmir regions and West Bengal (map A-2). Map B-1, shows nearly 69 out of the 707 districts as hotspots for child anaemia, with a substantial concentration in areas characterised by a predominantly rural population. These districts span Jammu and Kashmir, Himachal Pradesh, Gujarat, Odisha, Chhattisgarh, Jharkhand, West Bengal, Assam and Tripura. However, only 21 districts were highly significant (p = 0.001) followed by 46 and 98 districts with p-values of 0.01 and 0.05, respectively (map B-2). About 101 out of the 707 districts formed hotspots for child anaemia linked to uneducated mothers in India. These hotspots included states such as Uttar Pradesh, Madhya Pradesh, Maharashtra, Bihar, West Bengal and specific regions in Jammu and Kashmir, Gujarat, Odisha, Telangana, Andhra Pradesh and Jharkhand (map C-1). In this, highly significant districts were concentrated in the southern region of Kerala, Tamil Nadu and also a few districts of northern regions like Uttar Pradesh, Bihar etc (map C-2). Nearly 48 out of the 707 districts have been identified as hotspots for child anaemia associated with the Muslim religion, covering areas in Jammu and Kashmir, Ladakh, West Bengal and Assam. Also, districts in the Jammu and Kashmir region and eastern regions like Orissa etc were highly significant (map D-1 and D-2).

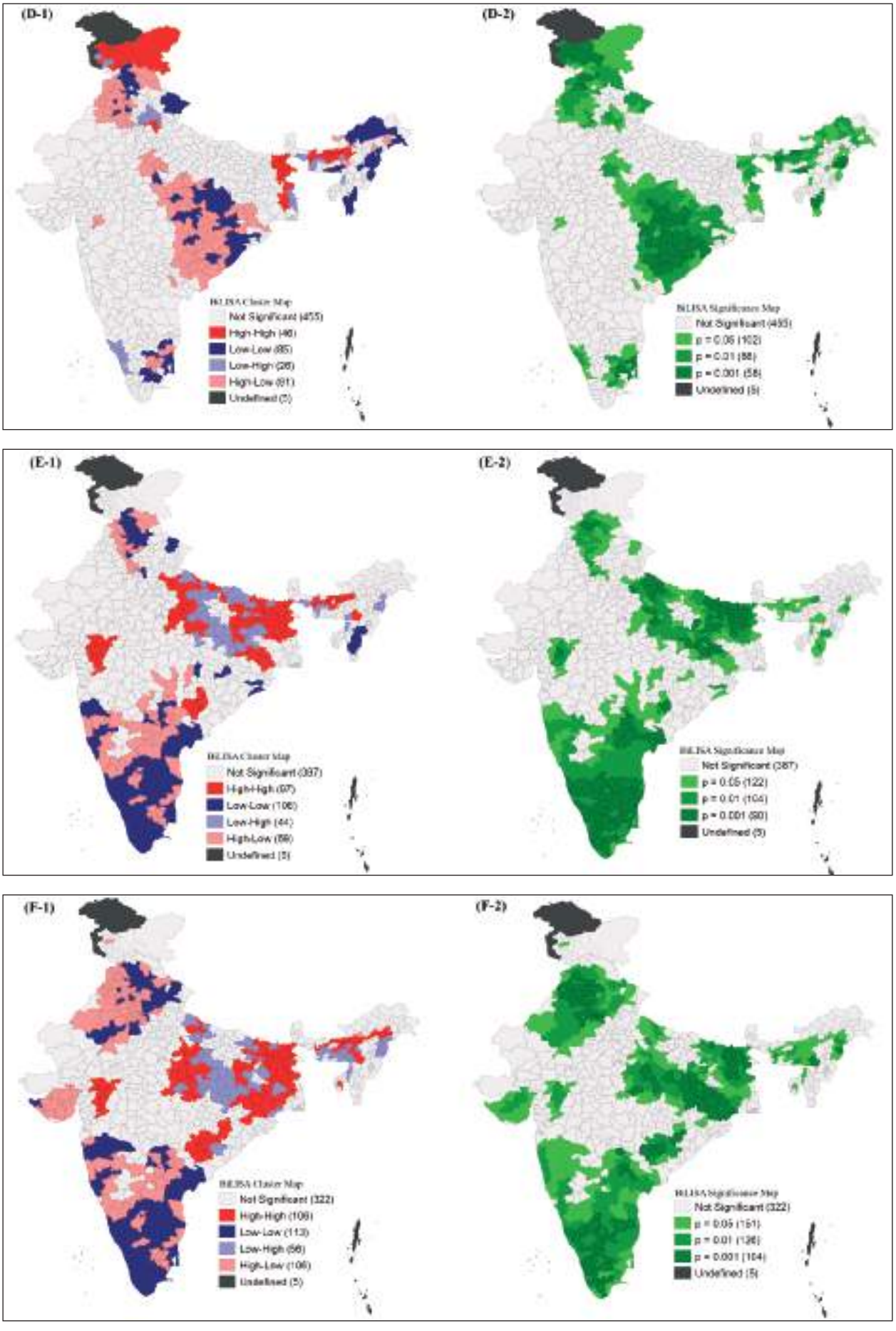
Out of the 707 districts, 97 have been pinpointed as hotspots due to a lack of media exposure, while 106 districts have been identified as hotspots based on the poorest wealth index. These hotspots were distributed across both the western and eastern parts of India, encompassing regions such as Gujarat, Odisha, West Bengal and certain districts in Haryana, Punjab, Bihar and Assam (map E-1, F-1).

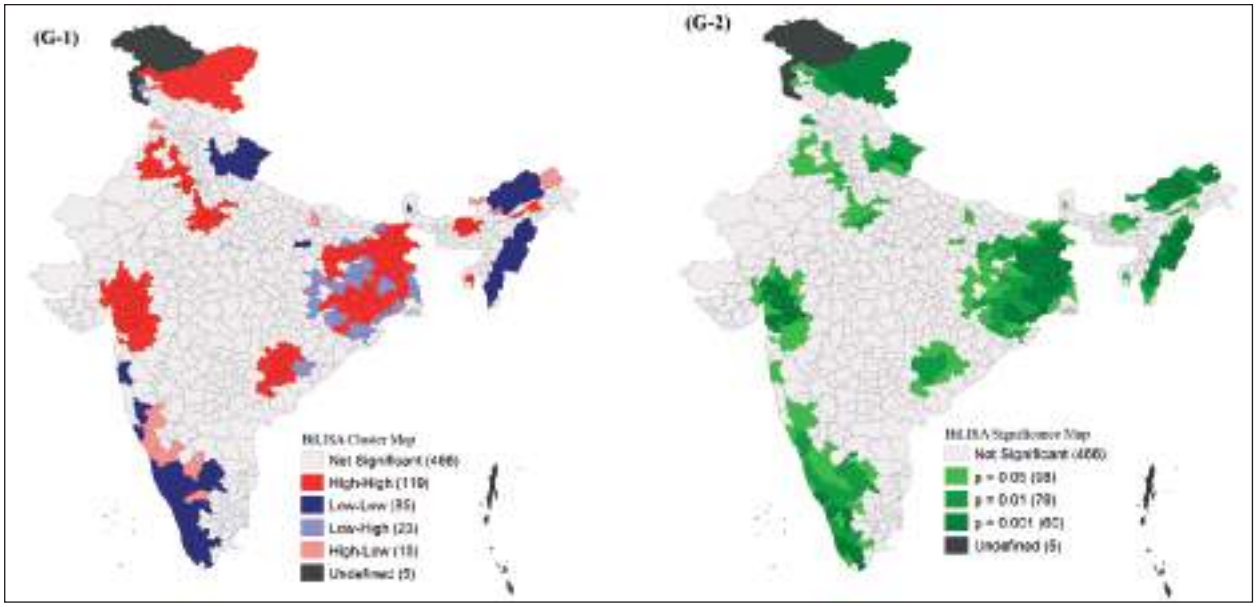
Almost 119 out of the 707 districts have emerged as hotspots for child anaemia and anaemic mothers, including the states of Ladakh, Jammu and Kashmir, Punjab, Delhi, Haryana, Gujarat, Andhra Pradesh, Odisha, Jharkhand, West Bengal, Bihar, and specific districts in Assam and Tripura (map G-1). Out of these 60 districts were highly significant (p = 0.001) which are mostly concentrated in the Ladakh region and eastern and northeastern states (map G-2).

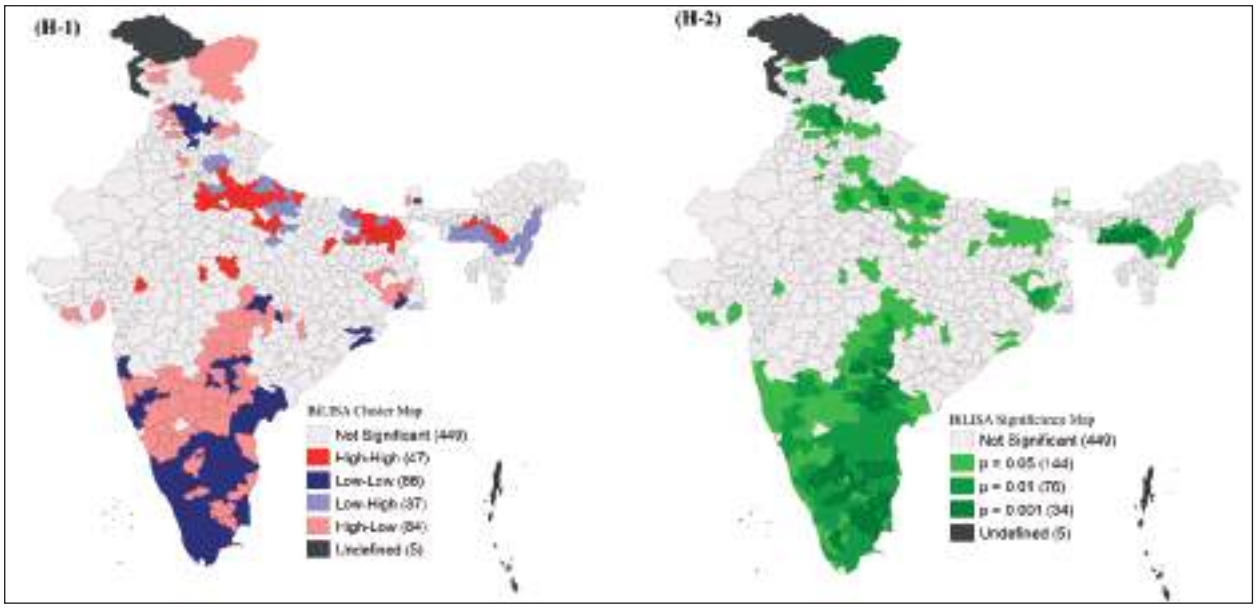
Among the 707 districts, 47 have been identified as hotspots in terms of higher birth order children (map H-1), while 17 districts and 68 dis-

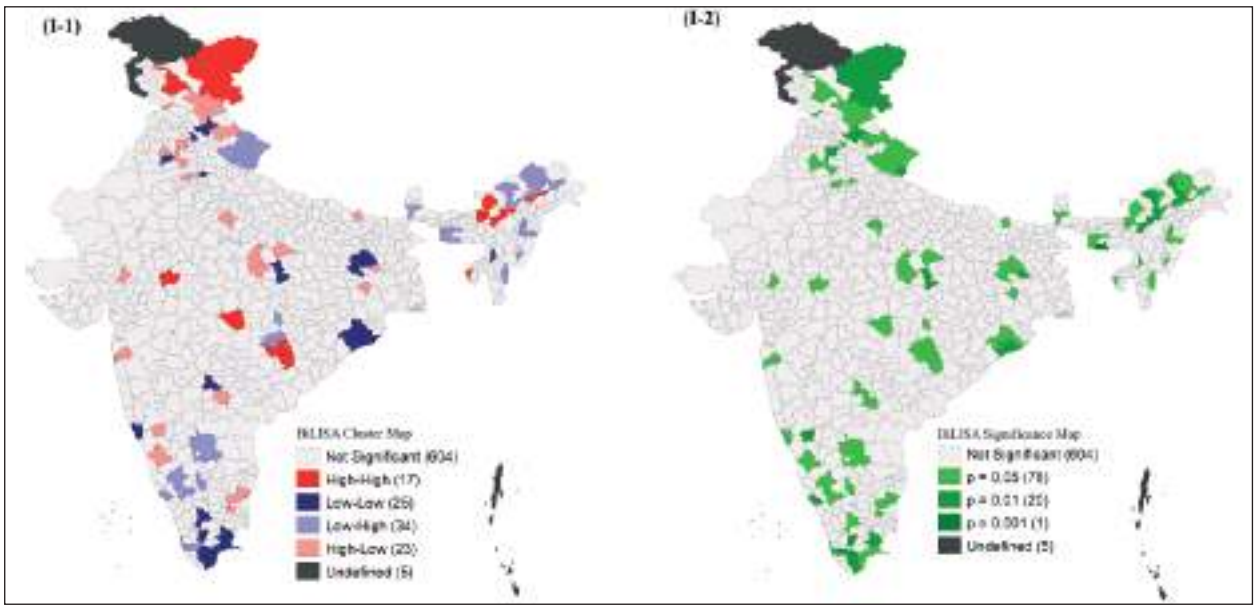
CONTENT


(A-1)
BiLISA Cluster Map
Not Significant (460)
High-High (82)
Low-Low (88)
Low-High (28)
High-Low (85)
Undefined (5)
(A-2)
BiLISA Significance map
Not Significant (460)
p = 0.05 (131)
p = 0.01 (70)
p = 0.001 (42)
Undefined (5)
(B-1)
(B-2)
(C-1)
Not Significant (414)
High-High (101)
Low-Low (104)
(C-2)
Not Significant (414)
p = 0.05 (116)
p = 0.01 (86)
p = 0.001 (63)
Undefined (5)


(D-1)
Not Significant (455)
High-High (46)
Low-Low (85)
Low-High (26)
High-Low (91)
Undefined (5)
(D-2)
Not Significant (493)
p = 0.05 (102)
p = 0.01 (88)
p = 0.001 (58)
Undefined (5)
(E-1)
Not Significant (397)
High-High (97)
Low-Low (106)
Low-High (44)
High-Low (59)
Undefined (5)
(E-2)
Not Significant (387)
p = 0.05 (122)
p = 0.01 (104)
p = 0.001 (80)
Undefined (5)
(F-1)
Not Significant (322)
High-High (109)
Low-Low (113)
Low-High (56)
High-Low (106)
Undefined (5)
(F-2)
Not Significant (322)
p = 0.05 (151)
p = 0.01 (126)
p = 0.001 (104)
Undefined (5)


(G-1)
BiLISA Cluster Map
Not Significant (466)
High-High (119)
Low-Low (85)
Low-High (23)
High-Low (15)
Undefined (5)
(G-2)
BiLISA Significance Map
Not Significant (466)
p = 0.05 (98)
p = 0.01 (78)
p = 0.001 (60)
Undefined (5)


(H-1)
BiLISA Cluster Map
Not Significant (449)
High-High (47)
Low-Low (88)
Low-High (97)
High-Low (84)
Undefined (5)
(H-2)
BiLISA Significance Map
Not Significant (449)
p = 0.05 (144)
p = 0.01 (76)
p = 0.001 (34)
Undefined (5)


(I-1)
BiLISA Cluster Map
Not Significant (604)
High-High (17)
Low-Low (25)
Low-High (34)
High-Low (25)
Undefined (5)
(I-2)
BiLISA Significance Map
Not Significant (604)
p = 0.05 (78)
p = 0.01 (25)
p = 0.001 (1)
Undefined (5)

CONTENT

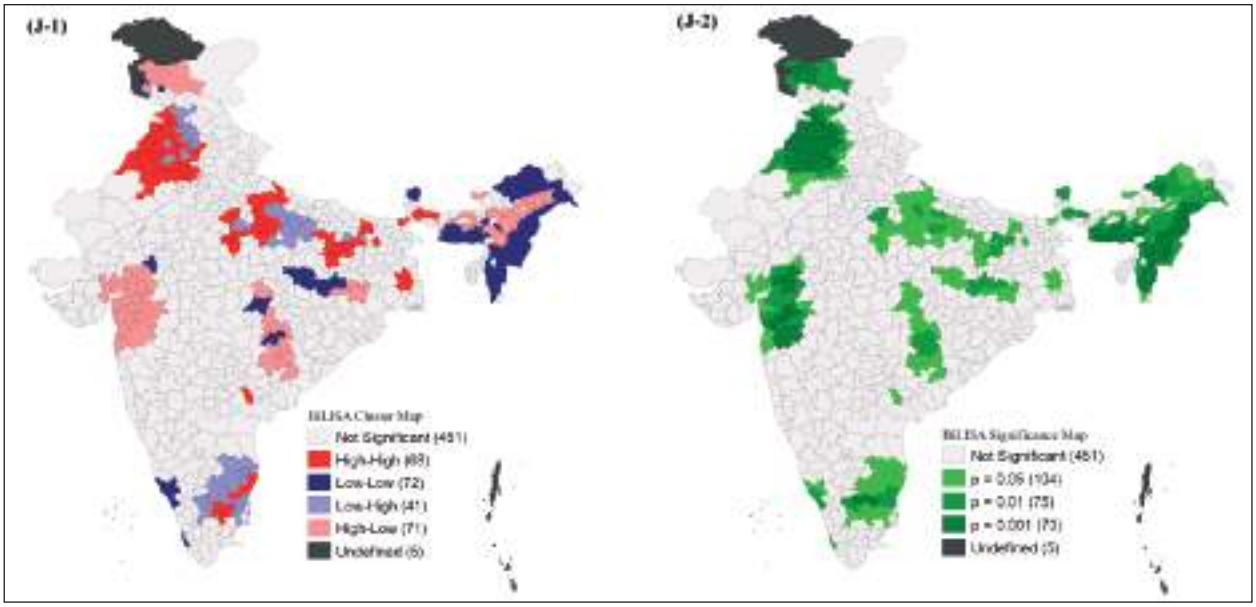


Figure 3: Bivariate local indicator of spatial association (LISA) cluster map and significance map of child anaemia with selected predictor variables

LISA cluster map: light grey: not significant; dark red: high-high; dark blue: low-low; light blue: low-high; light red: high-low; dark grey: undefined;
LISA significance map: light grey: not significant; light green: p = 0.05; green: p = 0.01; dark green: p = 0.001; dark grey: undefined;
Child anaemia related to: A: mother age (15-19); B: residence (rural); C: education of mother (no education); D: religion (Muslim); E: media exposure (no exposure); F: wealth index (poorest); G: anaemia in mothers (yes); H: birth order (higher); I: gender (female); J: Caste (schedule caste);

Table 2: Result of the ordinary least square (OLS) model and spatial error model (SEM) assessing determinants of child anaemia in districts of India, NFHS-5 (2019–21)

Indicators	OLS		SEM	
	Coeff	p-value	Coeff	p-value
% Mother age (15-19 years)	0.067	0.731	0.195	0.374
% Rural population	-0.007	0.699	-0.024	0.192
% Uneducated mother	0.289 *	0.000	0.225 *	0.000
% Muslim religion	-0.017	0.351	0.012	0.609
% No media exposure	0.129 *	0.002	0.069	0.117
% Poorest wealth index	-0.199 *	0.000	0.094 *	0.009
% Mother anaemia	0.594 *	0.000	0.531 *	0.000
% Birth order (≥ 6th)	-0.696 *	0.000	0.357 *	0.020
% Female child	-0.027	0.772	-0.030	0.699
% SC population	-0.022	0.453	0.051	0.154

**significant at α = 5 %; Coeff: coefficient; Akaike information criterion (AIC) value = OLS: 5036.11, SEM: 4875.26; LAMBDA: SEM: 0.597; R^2 = OLS: 0.526; SEM: 0.652; SC: schedule caste;*

tricts have been designated as hotspots concerning female children and SC populations, (map I-1, J-1) respectively.

Table 2 shows spatial regression models namely the OLS model and SEM to determine a special dependence of various predictors on child anaemia at the district level in India. The Akaike information criterion (AIC) value of the special error model came out to be 4875.26, which was comparatively lower than the OLS model. Hence this model better fitted the predictors for the explained variable. The SEM revealed that a 10 % increase in the proportion of uneducated mothers in a district, resulted in a 2.2 % increment in child anaemia (Coefficient (Coeff) = 0.225; $p < 0.05$). Similarly, a 10 % rise in the poorest wealth index within a district led to a 0.09 % increase in child anaemia (Coeff = 0.094; $p < 0.05$). Additionally, anaemic mothers significantly contributed as a risk factor for child anaemia in a district; for example, there was a 5.3 % increase in child anaemia for every 10 % rise in the proportion of mothers with anaemia in a particular district (Coeff = 0.531; $p < 0.05$). Among other predictors, a higher childbirth order was a notable risk factor for child anaemia in a district (Coeff = 0.357; $p < 0.05$).

Discussion

Analysis of NFHS-5 (2019-21) data has unveiled several significant determinants of childhood anaemia in India like anaemia status of mothers, mother age, maternal education, birth order, media exposure, wealth quantile etc. Some scholars have suggested the existence of multiple pathways linking childhood anaemia to the iron status of both children and their mothers.[21] For instance, antenatal anaemia can affect birth weight

CONTENT

and increase the risk of premature deliveries, a key factor in childhood anaemia.[22]

Maternal age showed a significant effect on anaemia status of their children. Mothers age (35 years and above) showed a protective effect for anaemia in children. This could be due to low maternal age contributing to low birth weight (LBW) babies, in turn, LBW in children might contribute to low haemoglobin levels thus resulting in anaemia.[23-26] Supporting presented findings, conclusions from other studies also suggest that women with a low educational level are more likely to have anaemic children, highlighting a significant association between education and anaemia.[27-29] This could be because the mother's level of education, influences the practices related to the child's health care.[30, 31] This study highlights statistically significant associations between household wealth and anaemia.

Presented study shows Hindu and Muslim women were more likely to anaemic children compared to women of other religion. Also, likelihood of child anaemia is higher in SC and ST categories against other castes. Social factors were found to be significantly associated with the prevalence of anaemia among children reported by other studies as well. This could be due to the limited educational opportunities, discrimination and social inequality which affect the awareness about healthcare practices and nutrition among SC and ST communities.[32-34]

In this study it was observed that, children with lower birth orders were less likely to be anaemic compared to those with higher birth order, which is supported by various other studies as well.[35, 36] This could be because an increase in the number of children associated with increased health problems due to competition for food, infections and cross contaminations.[34]

This study also indicated that children from mothers with no media exposure were more likely be anaemic compared to those from mothers with media exposure. This finding is supported by other studies where children from mothers with no media exposure were more likely to report anaemia compared to their counterparts.[34, 36] The reason could be that the mothers' media exposure may affect childcare practices through enhancing the knowledge of mothers on child feeding activities, disease prevention practices and improving health-seeking behaviours.[37]

Presented study observed that trend and pattern was the same over different states but varied slightly in magnitude. Severe anaemia prevalence was seen among western and central zone states. The states identified were Gujarat, Rajasthan, Madhya Pradesh, Haryana, Jammu and Kashmir, Karnataka and Maharashtra. More focus should be placed on these states. In this study child anaemia also exhibited a positive autocorrelation with its covariates among Indian districts, with hotspots identified in the western and central regions, including states such as Gujarat, Rajasthan, Madhya Pradesh, Haryana, Jammu and Kashmir, Ladakh and certain districts in Uttar Pradesh, Bihar, West Bengal, Odisha and Andhra Pradesh. These findings are consistent with a district-level study in India, which observed similar patterns and hotspot regions for child anaemia.[25]

These analyses provide region-specific spatial information which can help in decision-making, policy formulation and effective assessment of anaemia prevention and control among children. The current study has however a few limitations that need to be acknowledged. Firstly, the NFHS dataset lacked information on the underlying causes of anaemia, precluding their inclusion in analysis. Secondly, haemoglobin levels were measured using the battery-operated portable *HemoCue Hb 201+* analyser, which raised concerns about its accuracy compared to lab-based methods. Future research in this area is recommended to explore this association and gain a more profound understanding of its implications.

Conclusion

Several important issues emerged from the study such as maternal education, socio-economic status, media exposer etc were found to be key factors of childhood anaemia in India. The present study does not only contribute to highlighting remarkable factors affecting the anaemia in children but also examines the geographical variations in anaemia. Comprehensive intervention strategies such as educating mothers, specially residing in rural areas about the harmful impacts of anaemia should be implemented and should target the hot spot districts with the highest prevalence of anaemia.

Ethics

This study was a secondary analysis based on the currently existing dataset from the recent NFHS-5 survey with no identifiable information on the survey participants and did not directly involve with human participants or experimental animals. NFHS-5 obtained the consent before and during the survey. This dataset is available in the public domain for research use, therefore the ethics approval was not required in this paper.

Acknowledgement

None.

Conflicts of interest

The authors declare that there is no conflict of interest.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Data access

The data can be accessed from the DHS website at: https://dhsprogram.com/data/.

Author ORCID numbers

Abhijeet Joshi (AJ):
0000-0003-3584-445X
Deepak Tanwar (DT):
0000-0003-0398-313X
Pawan Kumar Dubey (PKD):
0000-0003-1871-3546
Mukesh Vishwakarma (MV):
0000-0003-1517-6992
Sabrina Sultana Rahman (SSR):
0009-0008-2850-2260

Author contributions

Conceptualisation: AJ, DT
Methodology: PKD
Software: MV
Validation: PKD
Formal analysis: MV, PKD
Resources: SSR
Data curation: SSR
Writing - original draft: AJ, PKD, MV
Writing - review and editing: PKD, MV
Visualisation: PKD, MV
Supervision: DT

References

1. Kapil U, Kapil R, Gupta A. National Iron Plus Initiative: current status & future strategy. The Indian journal of medical research. 2019 Sep;150(3):239. doi: 10.4103/ijmr.ijmr_1782_18.
2. Habte D, Asrat K, Magafu MG, Ali IM, Benti T, Abtew W, et al. Maternal risk factors for childhood anaemia in Ethiopia. Afr J Reproduc Health. 2013 Sep 1;17(3):110-8. PMID: 24069773.
3. World Health Organization. Anemia. [Internet]. [Cited: 1 Jan 2023]. Available at: https://www.who.int/health-topics/anaemia.
4. Anand T, Rahi M, Sharma P, Ingle GK. Issues in prevention of iron deficiency anemia in India. Nutrition. 2014 Jul 1;30(7-8):764-70. doi: 10.1016/j.nut.2013.11.022.
5. Thankachan P, Walczyk T, Muthayya S, Kurpad AV, Hurrell RF. Iron absorption in young Indian women: the interaction of iron status with the influence of tea and ascorbic acid. Am J Clin Nutr. 2008 Apr;87(4):881-6. doi: 10.1093/ajcn/87.4.881.
6. Calis JC, Phiri KS, Faragher EB, Brabin BJ, Bates I, Cuevas LE, et al. Severe anemia in Malawian children. N Engl J Med. 2008 Feb 28;358(9):888-99. doi: 10.1056/NEJMoa072727.
7. Schneider JM, Fujii ML, Lamp CL, Lönnerdal B, Dewey KG, Zidenberg-Cherr S. Anemia, iron deficiency, and iron deficiency anemia in 12-36-mo-old children from low-income families. Am J Clin Nutr. 2005 Dec;82(6):1269-75. doi: 10.1093/ajcn/82.6.1269.
8. International Institute for Population Sciences (IIPS) and ICF, 2021. National Family Health Survey (NFHS-5), 2019–21: India. [Internet]. [Cited: 1 Jan 2023]. Available at: https://main.mohfw.gov.in/sites/default/files/NFHS-5_Phase-II_0.pdf.
9. Kalaivani K, Ramachandran P. Time trends in prevalence of anaemia in pregnancy. Indian J Med Res. 2018 Mar;147(3):268-77. doi: 10.4103/ijmr.IJMR_1730_16.
10. Subramaniam G, Girish M. Iron deficiency anemia in children. Indian J Pediatr. 2015 Jun;82:558-64. doi: 10.1007/s12098-014-1643-9.
11. Sekhar DL, Murray-Kolb LE, Kunselman AR, Weisman CS, Paul IM. Association between menarche and iron deficiency in non-anemic young women. PloS One. 2017 May 9;12(5):e0177183. doi: 10.1371/journal.pone.0177183.
12. Bentley ME, Griffiths PL. The burden of anemia among women in India. Eur J Clin Nutr. 2003 Jan;57(1):52-60. doi: 10.1038/sj.ejcn.1601504.

CONTENT

13. Kedar PS, Harigae H, Ito E, Muramatsu H, Kojima S, Okuno Y, et al. Study of pathophysiology and molecular characterization of congenital anemia in India using targeted next-generation sequencing approach. Int J Hematol. 2019 Nov;110:618-26. doi: 10.1007/s12185-019-02716-9.
14. Anselin L. Thirty years of spatial econometrics. Pap Reg Sci. 2010 Mar;89(1):3-25. doi: 10.1111/j.1435-5957.2010.00279.x
15. Getis A, Ord JK. The analysis of spatial association by use of distance statistics. Geogr Anal. 1992 Jul;24(3):189-206. doi: 10.1111/j.1538-4632.1992.tb00261.x.
16. Getis A, Ord JK, Anselin L, Rey SJ. Perspectives on spatial data analysis. Berlin, Germany: Springer; 2010. doi: 10.1007/978-3-642-01976-0.
17. Anselin L. Local indicators of spatial association—LISA. Geogr Anal. 1995 Apr;27(2):93-115. doi: 10.1111/j.1538-4632.1995.tb00338.x
18. Clark PJ, Evans FC. Distance to nearest neighbour as a measure of spatial relationships in populations. Ecology. 1954 Oct 1;35(4):445-53. doi: 10.2307/1931034.
19. Cliff AD, Ord K. Spatial autocorrelation: a review of existing and new measures with applications. Econ Geogr. 1970 Jun 1;46(sup1):269-92. doi: 10.2307/143144.
20. Anselin L. Spatial regression. The SAGE handbook of spatial analysis. California, USA: SAGE Publications, Ltd 2009;1:255-76. doi: 10.4135/9780857020130.
21. Pasricha SR, Black J, Muthayya S, Shet A, Bhat V, Nagaraj S, et al. Determinants of anemia among young children in rural India. Pediatrics. 2010 Jul 1;126(1):e140-9. doi: 10.1542/peds.2009-3108.
22. Wharton BA. Iron deficiency in children: detection and prevention. Br J Haematol. 1999 Aug;106(2):270-80. doi: 10.1046/j.1365-2141.1999.01511.x.
23. Chen K, Zhang X, Li TY, Chen L, Qu P, Liu YX. Co-assessment of iron, vitamin A and growth status to investigate anemia in preschool children in suburb Chongqing, China. World J Pediatr. 2009 Nov;5:275-81. doi: 10.1007/s12519-009-0052-z.
24. Skalicky A, Meyers AF, Adams WG, Yang Z, Cook JT, Frank DA. Child food insecurity and iron deficiency anemia in low-income infants and toddlers in the United States. Matern Child Health J. 2006 Mar;10(2):177-85. doi: 10.1007/s10995-005-0036-0.
25. Rutstein SO, Kiersten J. The DHS Wealth Index. Calverton, Maryland. Report; 2004. doi: 10.13140/2.1.2806.4809.
26. Bhutta ZA, Das JK, Rizvi A, Gaffey MF, Walker N, Horton S, et al. Evidence-based interventions for improvement of maternal and child nutrition: what can be done and at what cost? Lancet. 2013 Aug 3;382(9890):452-77. doi: 10.1016/S0140-6736(13)60996-4.
27. Sharma H, Singh SK, Srivastava S. Socio-economic inequality and spatial heterogeneity in anaemia among children in India: Evidence from NFHS-4 (2015–16). Clin Epidemiol Glob Health. 2020 Dec 1;8(4):1158-71. doi: 10.1016/j.cegh.2020.04.009.
28. Mehrotra M, Yadav S, Deshpande A, Mehrotra H. A study of the prevalence of anemia and associated sociodemographic factors in pregnant women in Port Blair, Andaman and Nicobar Islands. J Family Med Prim Care. 2018 Nov-Dec;7(6):1288-93. doi: 10.4103/jfmpc.jfmpc_139_18.
29. Ngesa O, Mwambi H. Prevalence and risk factors of anaemia among children aged between 6 months and 14 years in Kenya. PLoS One. 2014 Nov 25;9(11):e113756. doi: 10.1371/journal.pone.0113756.
30. Desai S, Alva S. Maternal education and child health: Is there a strong causal relationship?. Demography. 1998 Feb 1;35(1):71-81. PMID: 9512911.
31. Paul S, Paul S, Gupta AK, James KS. Maternal education, health care system and child health: Evidence from India. Soc Sci Med. 2022 Mar;296:114740. doi: 10.1016/j.socscimed.2022.11474.
32. Kumar P, Chauhan S, Patel R, Srivastava S. Anaemia among mother-father-child pairs in India: examining co-existence of triple burden of anaemia in a family. BMC Public Health. 2021 Dec;21(1):1-8. doi: 10.1186/s12889-021-11408-1.
33. Ghosh K, Desai GS. Prevalence and detecting spatial clustering of anaemia among children 6–59 months in the districts of India. Clin Epidemiol Glob Health. 2021 Oct 1;12:100845. doi: 10.1016/j.cegh.2021.100845
34. Anteneh ZA, Van Geertruyden JP. Spatial variations and determinants of anemia among under-five children in Ethiopia, EDHS 2005–2016. Plos One. 2021 Apr 1;16(4):e0249412. doi: 10.1371/journal.pone.0249412.
35. Melku M, Alene KA, Terefe B, Enawgaw B, Biadgo B, Abebe M, et al. Anemia severity among children aged 6–59 months in Gondar town, Ethiopia: a community-based cross-sectional study. Ital J Pediatr. 2018 Sep 3;44(1):107. doi: 10.1186/s13052-018-0547-0.
36. Gebremeskel MG, Tirore LL. Factors associated with anemia among children 6–23 months of age in Ethiopia: a multilevel analysis of data from the 2016 Ethiopia demographic and health survey. Pediatric Health Med Ther. 2020 Sep 16;11:347-57. doi: 10.2147/PHMT.S258114.
37. Simieneh MM, Mengistu MY, Gelagay AA, Gebeyehu MT. Mothers' health care seeking behavior and associated factors for common childhood illnesses, Northwest Ethiopia: community based cross-sectional study. BMC Health Serv Res. 2019 Jan 23;19(1):59. doi: 10.1186/s12913-019-3897-4.

Pohan et al. Scr Med. 2024 Mar-Apr;55(2):149-56. DOI:10.5937/scriptamed55-48753

ORIGINAL ARTICLE

Correlation of the Caring Behaviour of Nurses With the Motivation of Patients Undergoing Haemodialysis

Vivi Yosafianti Pohan,[1] Arief Yanto,[1] Satriya Pranata[1]

Abstract

Background/Aim: There is a need to establish a satisfactory level of performance for nurses working in haemodialysis units, which will provide qualified competent nurses who will take care of patients. Thus, the purpose of this study was to analyse the caring behaviour of haemodialysis nurses with the motivation of patients undergoing haemodialysis.
Methods: The research design was a descriptive correlation approach. The subjects of this study were patients who were undergoing therapy in the haemodialysis room. Researchers collected data for 1 month in September 2023. The relationship between nurses' caring behaviour and haemodialysis patient motivation was determined by conducting a Spearman rank correlation analysis.
Results: Out of 118 patients, 48.7 % of patients thought nurses had poor caring behaviour. The research results also showed that patient motivation in undergoing haemodialysis was in the low motivation category (47.8 %). There was a significant relationship between nurses' caring behaviour and patient motivation in undergoing haemodialysis therapy (p = 0.0001). Based on the correlation coefficient value (r = 0.632), the two variables had a strong relationship.
Conclusion: Nurses' caring behaviour can increase patient motivation in undergoing haemodialysis therapy. Nurses' caring behaviour still needs to be optimised because the interaction between nurses and patients in the treatment process provides support to patients.

Key words: Motivation; Haemodialysis; Caring; Behaviour.

1. Department of Nursing, Faculty of Nursing and Health Sciences, Universitas Muhammadiyah Semarang, Semarang, Central Java, Indonesia.

Citation:
Pohan VY, Yanto A, Pranata S. Correlation of the caring behaviour of nurses with the motivation of patients undergoing haemodialysis. Scr Med. 2024 Mar-Apr;55(2):149-56.

Corresponding author:
VIVI YOSAFIANTI POHAN
E: vyp@unimus.ac.id

Received: 16 January 2024
Revision received: 23 February 2024
Accepted: 24 February 2024

Introduction

The motivation of patients undergoing haemodialysis is essential to consider various factors that influence their experiences and outcomes. Studies have shown that patients undergoing haemodialysis face numerous challenges, including physical, psychological and socioeconomic issues.[1, 2] These challenges can impact their quality of life and overall well-being.[3, 4] Furthermore, the process of transitioning to haemodialysis presents a significant challenge for patients, as it involves accepting and adapting to the treatment.[5] This highlights the importance of understanding the factors that influence patients' responses to haemodialysis, including their demographic and medical characteristics.[6–8]

In addition to the challenges associated with haemodialysis, patients may experience stress and fatigue, which can significantly impact their psychosocial adaptation and quality of life.[9, 10] Addressing stress responses and providing interventions to reduce stress can be crucial

Copyright © 2024 Pohan et al. This is an open access article distributed under the Creative Commons Attribution License (CC BY), which permits unrestricted use, distribution and reproduction in any medium, provided the original work is properly cited.

CONTENT

in improving patients' psychosocial adaptation and overall well-being.[5] Moreover, the impact of nurse-led nonpharmacological multidisciplinary holistic nursing care on fatigue in haemodialysis patients underscores the significance of comprehensive care in addressing patients' physical and mental health.[11, 12]

Furthermore, the influence of social support in patients undergoing maintenance haemodialysis has been highlighted, with studies showing that social support, coping style, marital status and family income significantly influence patients' post-traumatic growth levels.[9, 13] This emphasises the need for holistic support systems to address the multifaceted challenges faced by haemodialysis patients.

Moreover, the role of motivation in fluid management among chronic haemodialysis patients has been recognised, with interventions targeting motivational issues, patient knowledge, social support and accurate self-assessment of fluid status being crucial in improving fluid restriction adherence.[14–16] Additionally, the effects of motivational interviewing on the health status of haemodialysis patients have been explored, indicating that motivational interviewing can lead to changes in attitudes, beliefs and behaviours, ultimately improving patients' adherence to treatment regimens and health status.[6, 17]

Nurses play a significant role in providing holistic care to haemodialysis patients, addressing not only their physical needs but also their emotional and spiritual well-being.[7, 18] Addressing haemodialysis patients' spirituality in nursing care is an essential component of high-quality care and these patients wanted nephrology nurses to incorporate spirituality into their care by such means as supporting and maintaining their religious and spiritual resources and connections.[19]

Studies have shown that nurses are essential in providing support, maintaining religious and spiritual resources and establishing connections with patients, which can positively impact the patients' motivation to continue their treatment.[20, 21] Among haemodialysis professionals, nurses play an important role because they are near the patients, are more receptive to patients' concerns and can provide appropriate suggestions, advice or recommendations.[22, 23]

The intimate relationship between nurses and patients has been identified as a facilitator for the delivery of haemodialysis care, indicating that the caring behaviours of nurses can significantly influence patient motivation.[3, 24] Nursing presence is portrayed as "a caring behaviour of the nurse to be present with the patient in a clinical setting" to focus on the patient through attentiveness to the patient's needs and provide healing during haemodialysis treatment. Nurses play a major role in haemodialysis procedures because most of the complications facing patients during dialysis as hypotension, cramped muscles and weak pulse, need nurses with knowledge and practical experience.

Moreover, the provision of refined nursing intervention through caring behaviour has been shown to improve patient compliance, regulate negative emotions and enhance the nurse-patient relationship, all of which can contribute to patient motivation.[25] Therefore, there is a need to establish a satisfactory level of performance for nurses working in haemodialysis units which helps in providing qualified competent nurses who provide care for patients.

The purpose of this study was to analyse the caring behaviour of haemodialysis nurses with the motivation of clients undergoing haemodialysis.

Methods

The research design was a descriptive correlation approach. This study was completed in stages using descriptive methods with exploratory studies to obtain initial data which became a preliminary study.

Sample

This research was carried out in the haemodialysis room at Roemani Hospital, Semarang, Central Java, Indonesia. The research was conducted according to plan with research subjects of patients who were undergoing haemodialysis therapy, a total of 115 patients. The research subject criteria applied were patients who underwent haemodialysis more than once, could read and write and did not experience emergencies. The number of research subjects was calculated using the G-power program with an expected power of 95 % and a basic correlation

CONTENT

from previous research of 0.3. The sampling technique used was purposive sampling. This research was carried out in the haemodialysis treatment room at Roemani Hospital, Semarang, Indonesia.

Data collection

Researchers collected data for 1 month in September 2023. Data collection was carried out by giving questionnaires to research subjects while undergoing the haemodialysis process. Questionnaires that have been filled out by research subjects are checked for completeness by the researcher before the data entry.

Instruments

Caring for nurses was measured using a caring behaviour questionnaire adopted from a previous study.[26] The caring behaviour instrument consisted of 28 statement items which included: 10 creative elements of caring. This instrument has been declared valid from the results of the validity test with a value of r = 0.464-0.763 and declared reliable with a Cronbach's α = 0.944. Meanwhile, motivation variables were measured using questionnaires from other research. The questionnaire has been declared valid with a value of r = 0.468-0.662 and reliable with a Cronbach's α = 0.888.

Data analysis

The relationship between nurses' caring behaviour and haemodialysis patient motivation was determined by conducting a Spearman rank correlation analysis. This analysis was carried out due to a non-normal distribution of data. The research results were presented in the form of tables and graphic images to determine the direction of the relationship between the two variables. The data was analysed using the IBM SPSS Statistics version 26 programme.

Ethical considerations

Researchers explained prospective research subjects (patients) the aims and benefits of research. Patients who were willing to become research subjects were asked to sign the informed consent form that has been provided. Researchers did not include the identity of research subjects in reports or publication manuscripts to maintain subject confidentiality.

Results

The research results showed that the average age of the research subjects was 46.60 ± 7.35 years with the youngest being 30 years and the oldest being 62 years. The research subjects were dominated by male patients (77.4 %). Based on the research results (Table 1), it can be seen that nurses' caring behaviour still needed to be optimised. This is demonstrated by the results of patient assessments regarding nurses' caring behaviour which showed that 48.7 % of patients thought nurses had poor caring behaviour. Nurses' caring behaviour had an average score of 121.69 ± 14.61, with the lowest score being 84 and the highest score being 140.

The research results also showed that patient motivation in undergoing treatment, or the haemodialysis therapy process was in the low motivation category (47.8 %). Patient motivation in undergoing haemodialysis therapy had an average score of 69.80 ± 9.90, with the lowest score being 40 and the highest score being 80.

Table 1: Haemodialysis therapy patients gender, their motivation and perception of caring behaviour of nurses (n = 115)

Parameter	N	%
Gender of patients		
Man	89	77.4
Woman	26	22.6
Caring behaviour of nurses		
Good	59	51.3
Bad	56	48.7
Motivation of haemodialysis therapy in patients		
High	60	52.2
Low	55	47.8
Total	115	100.0

The relationship between nurses' caring behaviour and patient motivation in undergoing haemodialysis therapy was determined by conducting a correlation analysis between these two variables. Spearman correlation analysis (Table 2) showed that there was a significant relationship between nurses' caring behaviour and patient motivation in undergoing haemodialysis therapy (p = 0.0001). Based on the correlation coefficient value r = 0.632, it can be seen that the two variables had a strong relationship. The two variables studied had a unidirectional relationship, so it can be concluded

CONTENT

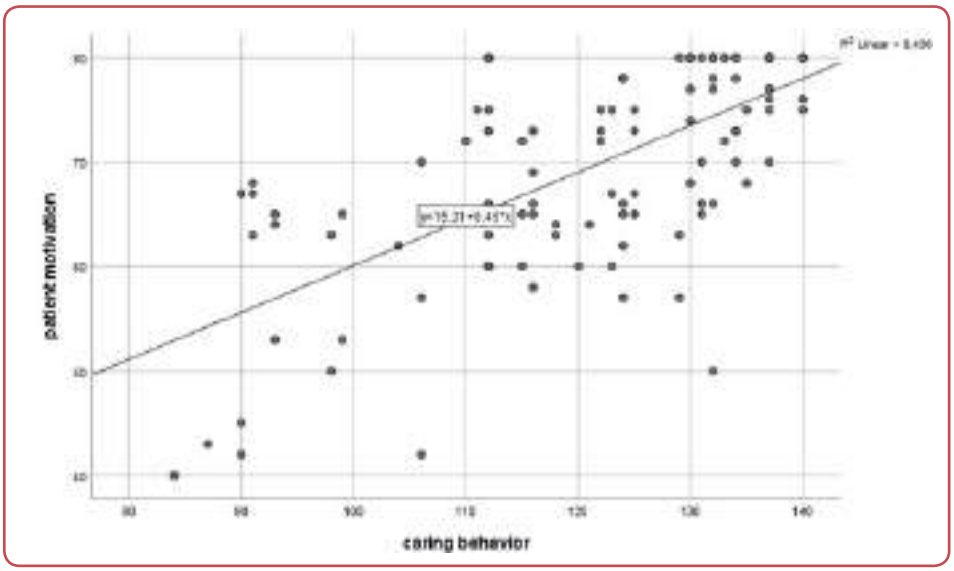


Figure 1: Relationship between nurses' caring behaviour and patient motivation in undergoing haemodialysis therapy

Table 2: Relationship between nurses' caring behaviour and motivation of haemodialysis therapy patients (n = 115)

Indicator		Motivation		r	p
		High	Low		
Nurses' caring behaviour					
	Good	44 (74.6 %)	15 (25.4 %)	0.632	0.0001[a]
	Bad	16 (28.6 %)	40 (71.4 %)		

[a]: Spearman Rank test; r: correlation coefficient, p: p-value, significant if < 0.05;

that the better the nurse's caring behaviour, the better the patient's motivation to undergo haemodialysis therapy in the hospital.

The research results (Figure 1) showed that the relationship between nurses' caring behaviour and patient motivation in undergoing haemodialysis therapy had a positive linear pattern. The results of the analysis showed that nurses' caring behaviour was able to increase patient motivation in undergoing haemodialysis therapy by 43.6 % and 56.4 % was influenced by other variables outside the research.

Discussion

The research results showed that the average age of patients undergoing haemodialysis therapy was 46.6 years. Another study also found the same thing the average age of haemodialysis patients was 46.85 years. However, another study reported that the cumulative incidence of death in home haemodialysis patients was 19.2 %, indicating that haemodialysis patients may also include older individuals.[2] Therefore, the average age of patients undergoing haemodialysis can range from the mid-40s to older ages, reflecting the diverse demographic characteristics of this patient population.[9]

Patients undergoing haemodialysis therapy are dominated by chronic kidney disease (CKD) sufferers. There are several factors thought to contribute to the high prevalence of CKD in individuals in their 40s. Risk factors such as diabetes mellitus, hyperuricaemia and obesity have been identified as significant contributors to the development of CKD.[2, 27, 28] Additionally, the presence of comorbidities such as diabetes mellitus and hypertension, which are common in middle-aged individuals, may increase the risk of CKD.[29] Additionally, a correlation between hypertension and the occurrence of CKD has been highlighted, indicating that individuals with hypertension, which often develops in middle age, may have a higher risk of developing CKD.[30, 31] Additionally, the potential impact of nutritional intake on CKD has been suggested, with lower haemoglobin levels identified as a potential factor contributing to fatigue in CKD patients. It is important to note that the prevalence of CKD in individuals in their 40s may also be influenced by lifestyle factors such as obesity and trauma, which may contribute to the development of conditions such as osteoarthritis and potentially impact kidney health.[32, 33] Additionally, the presence of other chronic conditions such as Graves' disease in younger individuals may

CONTENT

also contribute to the overall burden of kidney disease in this age group.[30] In summary, the high prevalence of CKD in individuals in their 40s may be due to a combination of risk factors such as diabetes mellitus, hyperuricaemia and obesity, as well as the presence of comorbidities such as hypertension and lifestyle factors such as obesity and trauma. These factors collectively contribute to the increased susceptibility of individuals in their 40s to developing CKD.[30, 34]

The research results showed that nurses' caring behaviour still needs to be optimised. This result is the same as other research which explains that nurses' caring behaviour is still low. This low caring behaviour of nurses can be influenced by several factors, both internal and external.[35] The low level of caring behaviour in nurses can be influenced by various factors. Research has shown that nurses' caring behaviour may be influenced by burnout, which can result from the emotional demands of providing care.[36] Additionally, the critical care environment and handling of patients with life-threatening conditions can impact nurses' caring behaviour. Factors such as nursing supervision, spirituality, caring efficacy and emotional intelligence were found to be significantly associated with nurses' caring behaviour in critical care settings. Burnout has also been identified as a factor that may influence empathy and, consequently, caring behaviour among nurses. Furthermore, the influence of the work environment, demographic factors and nurse-patient interpersonal relationships on caring behaviour has been highlighted in various studies.[37–39] Additionally, the presence of guilt and secondary traumatic stress has been associated with compassion fatigue among nurses, which may impact their caring behaviour.[37] The level of empathy, fatigue and impact of the COVID-19 pandemic were also found to influence nurses' caring behaviour. In addition, the quality of the nurse-patient relationship, empathy and the demands of the nursing profession have been identified as factors that can influence nurses' caring behaviour. The low level of caring behaviour among nurses may be influenced by interplaying factors such as work fatigue, work environment, nurse-patient relationship, empathy and the emotional demands of the nursing profession.[37, 40]

The research results also showed that patient motivation in undergoing treatment or the haemodialysis therapy process is still not optimal. The low motivation of haemodialysis patients has been linked to various factors identified in research. The need for prolonged haemodialysis treatment, associated complications and patient compliance requirements have been highlighted as factors influencing patient motivation.[41, 42] In addition, the relationship between employment status and fatigue in haemodialysis patients has been established, with a significant relationship between unemployment and the occurrence of fatigue. In addition, the prevalence of high levels of fatigue in haemodialysis patients has been reported, indicating the impact of fatigue on patient motivation. Physical complaints commonly expressed by haemodialysis patients, such as fatigue, intolerance to cold weather, pruritus, weakness in the lower extremities and difficulty sleeping, are also known to contribute to low motivation. Additionally, the impact of lack of physical activity on the high mortality rate in end-stage renal disease (ESRD) patients undergoing haemodialysis has been highlighted, indicating the potential influence of physical activity on patient motivation.[31, 43] The routine activity of haemodialysis as a renal replacement therapy for CKD patients has also been emphasised, highlighting the long-term and repetitive nature of the treatment, which can influence patient motivation. Additionally, the fear of haemodialysis among patients with low levels of education has been identified as a barrier to treatment adherence and motivation.[44] The low motivation of haemodialysis patients is associated with factors such as the need for prolonged treatment, employment status, fatigue, physical complaints, lack of physical activity, the routine nature of the treatment and fear of haemodialysis, all of which can have a significant impact on patients motivation.[43, 45]

The results of the study showed that there was a significant relationship between nurses' caring behaviour and patient motivation in undergoing haemodialysis therapy. The caring behaviour of nurses has a significant influence on the motivation of haemodialysis patients. Research has shown that nurses' caring behaviour, particularly expressive and relational behaviour was positively correlated with patient satisfaction.[12, 46] However, there may be a mismatch between patient and caregiver perceptions of caring, highlighting the importance of aligning these perceptions to improve patient motivation. In the context of haemodialysis, nurses' perceptions of the practice environment and patients' perceptions of nurses'

CONTENT

caring behaviour are closely related to patient satisfaction with nursing services. In addition, nursing interventions that identify and control haemodialysis patients' level of uncertainty can significantly improve patients' self-care coping and compliance.[47] The presence of nurses, which is defined as the caring behaviour of nurses present with patients in the clinical environment, plays an important role in focusing attention on patient needs and providing healing during haemodialysis treatment.[12] Additionally, nurses can contribute to effective fluid balance control, reduced costs and improved quality of care for haemodialysis patients through their nutritional knowledge.

Nurses play a key role in encouraging the development of self-care behaviour among haemodialysis patients by providing the necessary knowledge and skills.[23] The relationship between nurses and patients can facilitate the provision of haemodialysis services, emphasising the importance of intimate relationships between nurses and patients in increasing patient motivation.[25, 48] Additionally, nurses' experiences in implementing caring attitudes and behaviours in daily clinical practice have been observed to increase self-esteem, sense of personal accomplishment and job satisfaction.[46] It is also important for nurses to provide regular follow-ups and instructions to haemodialysis patients regarding self-care behaviours. The caring behaviour of nurses is closely related to patient motivation in the context of haemodialysis.[49]

Limitation of this study was that it was limited to only one City in Indonesia. It would be better if the study was conducted in many cities to achieve generalisation.

Conclusion

Nurses' caring behaviour can increase patient motivation in undergoing haemodialysis therapy. The interaction between nurses and patients in the treatment process can provide support to patients to face the therapy they are undergoing. Nurses are expected to always maintain quality in providing services to patients, especially to patients who are undergoing haemodialysis therapy in hospitals.

Ethics

The study was approved by the Health Research Ethics Committee of the Faculty of Nursing and Health Sciences, decision No 220/KEPK/VIII/2023, dated 28 August 2023.

Acknowledgement

The authors would like to thank Universitas Muhammadiyah Semarang for funding support.

Conflicts of interest

The authors declare that there is no conflict of interest.

Funding

This study was financially supported by the Universitas Muhammadiyah Semarang.

Data access

The data that support the findings of this study are available from the corresponding author upon reasonable individual request.

Author ORCID numbers

Vivi Yosafianti Pohan (VYP):
0000-0003-1974-6059
Arief Yanto (AY):
0000-0002-9033-9547
Satriya Pranata (SP):
0000-0002-2026-8931

Author contributions

Conceptualisation: VYP
Methodology: VYP

CONTENT

Validation: VYP
Formal analysis: VYP
Investigation: VYP
Resources: AY, SP
Data curation: AY, SP
Writing - original draft: VYP
Writing - review and editing: AY, SP
Visualisation: AY, SP
Supervision: VYP
Project administration: AY, SP
Funding acquisition: VYP

References

1. Sousa CN, Teles P, Sousa R, Cabrita F, Ribeiro OMPL, Delgado E, et al. Hemodialysis vascular access coordinator: Three-level model for access management. Semin Dial. 2024 Mar-Apr;37(2):85-90. doi: 10.1111/sdi.13153.
2. Wu HHL, Dhaygude AP, Mitra S, Tennankore KK. Home dialysis in older adults: challenges and solutions. Clin Kidney J. 2022;16(3):422-31. doi:10.1093/ckj/sfac220.
3. Utami SS, Erawati M, Dewi NS. Internal protective factors that affect the resilience of hemodialysis patients: scoping review. J Ber Ilmu Keperawatan. 2023;16(2):309-19. doi:10.23917/bik.v16i2.1738
4. Eghtedar S, Chalak Z, Parizad N, Alinezhad V. Training health-promoting behaviors based on pender's model on psychological well-being to hemodialysis patients. Nurs Midwifery J. 2022;20(4):344-58. doi:10.52547/unmf.20.4.344.
5. Xie C, Zhou L, Sun C, Zhang Y, Li Y. The cross-cultural adaptation and psychometric evaluation of a learned helplessness scale for maintenance hemodialysis patients in China (LHS-MHD-C). Res Nurs Health. 2023;46(2):251-62. doi:10.1002/nur.22298.
6. Kim H, Jeong IS, Cho MK. Effect of treatment adherence improvement program in hemodialysis patients: a systematic review and meta-analysis. Int J Environ Res Public Health. 2022;19(18):11657. doi:10.3390/ijerph191811657.
7. Abdel-Salam AA, Sharshour SM, Aziz SMAE. Effect of evidence based guidelines on nurses' performance and attitude regarding care of children undergoing plasmapheresis. Tanta Sci Nurs J. 2023;31(4):192-221. doi:10.21608/tsnj.2023.328678.
8. Yuliawati AN, Ratnasari PMD, Maharani NLPS. Quality of life in end-stage renal disease patients undergoing hemodialysis and its affecting factors in a hemodialysis unit of general hospital denpasar. Borneo J Pharm. 2023;6(3):320-9. doi:10.33084/bjop.v6i3.3907.
9. Alshammari B, Noble H, McAneney H, Alshammari F, O'Halloran P. Caregiver burden in informal caregivers of patients in Saudi Arabia receiving hemodialysis: a mixed-methods study. Healthcare. 2023;11(3):366. doi:10.3390/healthcare11030366.
10. Kemnitz M, Antonini M, Delmas P. Relationship among symptoms, quality of life, and complementary and alternative medicines use among patients undergoing hemodialysis in French-speaking Switzerland. BMC Complement Med Ther. 2023;23(1):174. doi:10.1186/s12906-023-04001-z.
11. Huang M, Lv A, Yang F, Tang Y, Li Y, Hua Y, et al. Impacts of cognition of exercise on physical activity participation in hemodialysis patients. Semin Dial. 2023;36(5):366-73. doi:10.1111/sdi.13138.
12. Bellier-Teichmann T, Roulet-Schwab D, Antonini M, Brandalesi V, O'Reilly L, Cara C, et al. Transformation of clinical nursing practice following a caring-based educational intervention: a qualitative perspective. SAGE Open Nurs. 2022;8:23779608221078100. doi:10.1177/23779608221078100.
13. Powathil GG, Kr A. The experience of living with a chronic illness: a qualitative study among end-stage renal disease patients. J Soc Work End Life Palliat Care. 2023;19(3):190-208. doi:10.1080/15524256.2023.2229034.
14. Bossola M, Pepe G, Antocicco M, Severino A, Di Stasio E. Interdialytic weight gain and educational/cognitive, counseling/behavioral and psychological/affective interventions in patients on chronic hemodialysis: a systematic review and meta-analysis. J Nephrol. 2022;35(8):1973-83. doi:10.1007/s40620-022-01450-6.
15. Monem RFA, Abdullah WH, Atallah HR, Henedy WM. Effect of nursing intervention on controlling interdialytic weight and vascular access complications among patients undergoing hemodialysis. Menoufia Nurs J. 2022;7(2):351-66. doi:10.21608/menj.2022.272898.
16. Sousa H, Ribeiro O, Costa E, Christensen AJ, Figueiredo D. Establishing the criterion validity of self-report measures of adherence in hemodialysis through associations with clinical biomarkers: A systematic review and meta-analysis. PLoS One. 2022;17(10):e0276163. doi:10.1371/journal.pone.0276163.
17. Alhamad A, Almulhim MY, Alburayh AA, Alsaad RA, Alhajji AM, Alnajjar JS, et al. Factors affecting adherence to hemodialysis therapy among patients with end-stage renal disease attending in-center hemodialysis in Al-Ahsa Region, Saudi Arabia. Cureus. 2023;15(10):e46701. doi:10.7759/cureus.46701.
18. Mailani F, Huriani E, Muthia R, Rahmiwati R. Self-management and relating factors among chronic kidney disease patients on hemodialysis: an Indonesian study. Nurse Media J Nurs. 2023;13(1):109-20. doi:10.14710/nmjn.v13i1.48708.
19. Nursalam N, Triharini M, Azza A, Chanif C, Wahyuni D, Machmudah M, et al. The relationship between spiritual quality and self- adaptation in cancer patients receiving chemotherapy. Scr Med. 2023;54(3):261-6. doi:10.5937/scriptamed54-44234.
20. Pranata S, Wu SFV, Purwadi H, Gede D, Putra S, Wulandari H. Exploring of self-management experience among health professional survivors from coronavirus disease 2019 in West Nusa Tenggara , Indonesia. 2021;9:19-27.doi:10.3889/oamjms.2021.6443.
21. Huda N, Nurchayati S, Pranata S, Sansuwito T. Religion and spirituality in coping with cancer : a literature review. 2022;14(October):40-45.doi:10.31674/mjn.2022.v14i02.025.
22. Gela D, Mengistu D. Self-management and associated factors among patients with end-stage renal disease undergoing hemodialysis at health facilities in Addis Ababa, Ethiopia. Int J Nephrol Renovasc Dis. 2018;11:329-36. doi:10.2147/IJNRD.S184671.

CONTENT

23. Havas K, Douglas C, Bonner A. Person-centred care in chronic kidney disease: a cross-sectional study of patients' desires for self-management support. BMC Nephrol. 2017;18(1):1-9. doi:10.1186/s12882-016-0416-2.
24. Jung WH, Kim HY. Promoting foot self-care in type 2 diabetes mellitus patients receiving hemodialysis based on the information-motivation-behavioral skills model. Nurs Health Sci. 2023;25(4):721-31. doi:10.1111/nhs.13067.
25. 25. Hejazi SS, Hosseini M, Ebadi A, Majd HA. Motivations for providing care in family caregivers of hemodialysis patients: A qualitative content analysis study. Iran J Heal Educ Heal Promot. 2022;10(1):58-69. doi:10.52547/ijhehp.10.1.58.
26. Tusnia D, Priyanti RP, Satus AS. [The correlation of work load with nurse 's caring behavior according to client 's perception at Igd Rsud Jombang]. J Ilm Keperawatan. 2017;3(2):30-36. Indonesian.
27. Wang SL, Chiu YW, Kung LF, Chen TH, Hsiao SM, Hsiao PN, et al. Patient assessment of chronic kidney disease self-care using the chronic kidney disease self-care scale in Taiwan. Nephrology (Carlton). 2019 Jun;24(6):615-21. doi: 10.1111/nep.13475.
28. Li H, Jiang Y fang, Lin CC. Factors associated with self-management by people undergoing hemodialysis: A descriptive study. Int J Nurs Stud. 2014;51(2):208-16. doi:10.1016/j.ijnurstu.2013.05.012.
29. Lai PC, Wu SV, Alizargar J, Pranata S, Tsai JM, Hsieh NC. Factors influencing self-efficacy and self-management among patients with pre-end-stage renal disease (Pre-ESRD). Healthcare (Basel). 2021 Mar 2;9(3):266. doi: 10.3390/healthcare9030266.
30. Agarwal R, Andersen MJ. Correlates of systolic hypertension in patients with chronic kidney disease. Hypertension. 2005;46(3):514-20. doi: 10.1161/01.HYP.0000178102.85718.66.
31. Liu X, Wang X, Ma H, Zhang W. Mechanisms underlying acupuncture therapy in chronic kidney disease: A narrative overview of preclinical studies and clinical trials. Front Nephrol. 2022;2:1006506. doi:10.3389/fneph.2022.1006506.
32. Hercz D, Jiang SH, Webster AC. Interventions for itch in people with advanced chronic kidney disease. Cochrane Database Syst Rev. 2020;2020(12):cd011393. doi:10.1002/14651858.CD011393.pub2.
33. Tsai MH, Hsu CY, Lin MY, Yen MF, Chen HH, Chiu YH, et al. Incidence, prevalence, and duration of chronic kidney disease in Taiwan: results from a community-based screening program of 106,094 individuals. Nephron. 2018;140(3):175-84. doi:10.1159/000491708.
34. Saffer T, Mesiwala A. Systematic CKD care approaches: a potential solution for the costly ESRD Program. Kidney Med. 2022;5(2):100581. doi:10.1016/j.xkme.2022.100581.
35. Soesanto E, Yanto A, Irani N, Pranata S, Rejeki S, Sasmito P. Job satisfaction among primary health care nurses. Int J Public Heal Sci. 2022;11(4):1416-23. doi:10.11591/ijphs.v11i4.21529.
36. Bjørk IT, Hamilton GA. Clinical decision making of nurses working in hospital settings. Nurs Res Pract. 2011;2011:1-8. doi:10.1155/2011/524918.
37. Wade R. Embedding the A-EQUIP model of restorative supervision in a critical care unit by professional nurse advocates. Br J Nurs. 2023;32(15):744-7. doi: 10.12968/bjon.2023.32.15.744.
38. Ahmed FR, Timmins F, Dias JM, Al-Yateem N, Gamil R, Subu MA, et al. Floating to intensive care units: Nurses' messages for instant action to promote patient safety. Nurs Crit Care. 2023 Nov;28(6):902-12. doi: 10.1111/nicc.12907.
39. Fallahnezhad T, Aghaie B, Norouzadeh R, Ebadi A, Abbasinia M. The challenges of nursing presence at the patient's bedside from the perspective of nurses: a qualitative study. Ethiop J Health Sci. 2023;33(2):281-90. doi:10.4314/ejhs.v33i2.13.
40. Le A, Lee MA, Wilson J. Nursing handoff education: An integrative literature review. Nurse Educ Pract. 2023;68:103570. doi:10.1016/j.nepr.2023.103570.
41. Wilson G, Ferrer J. 2005. Assessment and management of patients with vascular disorders and problems of peripheral circulation. In: Farrell M, Smeltzer SC, Bare BG, eds. Smetzer & Bare's textbook of medical-surgical nursing: First Australian/New Zealand Edition. Broadway, NSW, Australia: Lippincott Williams & Wilkins. pp. 819-857.
42. Sharifirad G, Azadbakht L, Feizi A, Kargar M, Mohebi S. Review the key role of self-efficacy in diabetes care. J Educ Health Promot. 2013;2(1):36. doi:10.4103/2277-9531.115827.
43. Sankar Raj VM, Patel P. The Role of a clinical psychologist in pediatric nephrology. Pediatr Clin North Am. 2022;69(5):941-9. doi:10.1016/j.pcl.2022.05.007.
44. Sharma S, Alexander KE, Green T, Wu ML, Bonner A. Energy conservation education intervention for people with end-stage kidney disease receiving haemodialysis (EVEREST): protocol for a cluster randomised control trial. BMJ Open. 2022;12(2):e056544. doi:10.1136/bmjopen-2021-056544.
45. Kalantar-Zadeh K, Lockwood MB, Rhee CM, Tantisattamo E, Andreoli S, Balducci A, et al. Patient-centred approaches for the management of unpleasant symptoms in kidney disease. Nat Rev Nephrol. 2022;18(3):185-98. doi:10.1038/s41581-021-00518-z.
46. Camedda C, Bici G, Magi CE, Guzzon A, Longobucco Y. The therapeutic nurse–patient relationship in hemodialysis: a pilot mixed-method study on the perceived quality of nurses' attitudes and caring behaviors. Nurs Reports. 2023;13(3):990-1003. doi:10.3390/nursrep13030087.
47. Sawma T, Sanjab Y. The association between sense of coherence and quality of life: a cross-sectional study in a sample of patients on hemodialysis. BMC Psychol. 2022;10(1):100. doi:10.1186/s40359-022-00805-9.
48. Murea M, Highland BR, Yang W, Dressler E, Russell GB. Patient-reported outcomes in a pilot clinical trial of twice-weekly hemodialysis start with adjuvant pharmacotherapy and transition to thrice-weekly hemodialysis vs conventional hemodialysis. BMC Nephrol. 2022;23(1):322. doi:10.1186/s12882-022-02946-w.
49. Asra A, Susila A, Rochman D, Rahayu TG, Lestari M. Adherence to hemodialysis therapy, self-efficacy and quality of life of chronic kidney disease patients in the hemodialysis room. KnE Soc Sci. 2023;8(14):16–24. doi:10.18502/kss.v8i14.13812.

CONTENT

Balakrishnan et al. Scr Med. 2024 Mar-Apr;55(2):157-63. DOI:10.5937/scriptamed55-47930

ORIGINAL ARTICLE

Association of Polymorphism (RS1800896) of IL-10 Gene and IL-10 Gene Expression in Ovarian Cancer Patients From Georgia

Pavithra Balakrishnan,[1] Jahnvi Shah,[1] Sandro Surmava,[1] Eka Kvaratskhelia,[1, 2] Elene Abzianidze,[1, 3] Nino Vardiashvili,[4] Ketevani Kankava[1]

Abstract

Background/Aim: Ovarian cancer is one of the most important causes of tumour-associated mortality and morbidity in women. Some genetic alterations, determining predisposition to ovarian cancer have already been identified, but these are mostly syndrome-associated cases, most ovarian tumours are still regarded as sporadic. The aim of this research was to identify new predisposing factors that might increase ovarian cancer risk. Genetic variants of IL-10 gene in patients with ovarian cancer was analysed.

Methods: Forty-eight patients with ovarian cancer along with 48 age-matched controls were included in the study. Single nucleotide polymorphism (SNP) genotyping and gene expression assays for IL-10 were performed using TaqMan assay (*Thermo Scientific*, USA). The selected SNP was rs1800896 upstream of IL-10 gene (IL-10-1082). All statistical analyses were performed by GraphPad Prism 9.3.1 for Mac.

Results: The genotype distributions of IL-10 gene polymorphisms among cancer and control groups were all according to the expected Hardy–Weinberg equilibrium. There was no statistically significant difference in frequency of genotypes and alleles between the two study groups ($p > 0.05$). In another analysis, the samples were grouped according to the polymorphic variant IL-10 (– 1082) A/G. Subjects having the homozygous variant (A/A) had lower IL-10 mRNA levels than those with the homozygous wild (G/G) genotype in both, ovarian cancer patients and controls, $p < 0.05$. mRNA levels on IL-10 were different among cases and controls ($p < 0.05$). Patients with ovarian cancer had higher level of mRNA for IL-10.

Conclusions: These results support the theory that IL-10 gene expression levels differ in patients with and without ovarian cancer. Polymorphic variant IL-10 (– 1082) A/G couldn't be confirmed to explain this difference in gene expression levels.

Key words: Ovarian cancer; Single nucleotide polymorphism (SNP); IL-10, Tumour microenvironment.

1. Department of Molecular and Medical Genetics, Tbilisi State Medical University, Tbilisi, Georgia.
2. Bakhutashvili Institute of Medical Biotechnology, Tbilisi State Medical University, Tbilisi, Georgia.
3. Ivane Beritashvili Centre of Experimental Biomedicine, Tbilisi, Georgia.
4. Inova Medical Centre, Tbilisi, Georgia.

Citation:
Balakrishnan P, Shah J, Surmava S, Kvaratskhelia E, Abzianidze E, Vardiashvili N, et al. Association of polymorphism (rs1800896) of IL-10 gene and IL-10 gene expression in ovarian cancer patients from Georgia. Scr Med. 2024 Mar-Apr;55(2):157-63.

Corresponding author:
EKA KVARATSKHELIA
E: e.kvaratskhelia@tsmu.edu
T: +995599298168

Received: 27 November 2023
Revision received: 23 February 2024
Accepted: 23 February 2024

Introduction

Being one of the most lethal malignancies, ovarian cancer represents the 3rd most common gynaecological cancer and the 8th most common cancer in women worldwide with a poor 5-year survival rate of 17 %.[1, 2] Over 3.1 million new cases and over 207,000 deaths were reported worldwide in 2020 alone.[2] Often it is diagnosed at late stage making it hard to achieve a good progno-

Copyright © 2024 Balakrishnan et al. This is an open access article distributed under the Creative Commons Attribution License (CC BY), which permits unrestricted use, distribution and reproduction in any medium, provided the original work is properly cited.

CONTENT

sis. Ovarian cancer is considered to demonstrate multifactorial causes including risk factors such as age, parity, obesity, smoking, etc. However, increasing evidence suggests that genetic factors contribute significantly to the incidence of ovarian cancer.[3] Most common mutations seen in ovarian cancer are in *TP53, BRCA1, BRCA2, KRAS* and *PIK3CA* genes.[4]

Tumour microenvironment (TME) plays a vital role in tumour cell survival and cancer progression, as well as determining the efficiency of administered chemotherapies and immunotherapies and consecutively the prognosis of the patients. Especially in ovarian cancer, due to a highly immunosuppressive microenvironment, the first line platinum-based drugs showed high recurrence rates and consequently became chemo-resistant. This leads to significant challenges in treatment modalities and patient recovery.[5] Multiple players of immune microenvironment of tumours have been studied in context of cancer risk or different biological behaviour of tumours. One of them is IL-10. Both, gene characteristic and protein expression levels of this cytokine are found to be altered in some tumour tissues of cancer patients. The IL-10 gene is located on chromosome 1q32.1 with 5 exons. About 40 SNPs have been described in the promoter region.[6]

The ovarian cancer patients showed significantly higher concentration of IL-10 cytokine in the ascites fluid and in the serum compared to the control group.[7] Even tumour biopsies showed a similar increase in IL-10 in tumour samples compared to normal ovarian tissue and normal ovaries.[8] The high expression of IL-10 is considered as a bad omen as it decreases the survival rates[9] and is shown to promote cancer cell migration which results in local spread and metastasis if present in ascites,[10] while some polymorphism in IL-10 gene promoter region showed to give advantageous results by providing optimal tumour debulking and disease free survival rates[11] and support tumour rejection by helping NK cells to activate against the tumour cells.[6]

This may suggest the possibility of IL-10 acting differently based on the presence of different cytokines and the result of which would reflect based on those other cytokines as well. Thus, knowledge about IL-10 could bear a new torch to understand the mechanisms of TME.

In the present study the single nucleotide polymorphism (SNP) rs1800896 also mentioned as the IL-10-1082A/G polymorphism in the IL-10 gene was analysed and the expression of IL-10 in the peripheral blood of ovarian cancer patients to check the extent of the role of this SNP in the ovarian cancer patients in Georgia.

Methods

The study design was a case-control study. Ovarian cancer patients who were consecutively admitted to the oncology department of Madison Hospital and Inova Medical Centre in Tbilisi, Georgia were recruited. Age-matched women who were regularly involved in cancer screening in an outpatient clinic in Tbilisi and were healthy, were asked to volunteer as control group members. Clinical information of patients was collected from medical notes.

The eligibility criteria for the cases were: a) diagnosis of ovarian carcinoma; b) ability to understand the purpose of the study and provide informed consent; c) being ethnically Georgian. Eligibility criteria for controls were as followed: no diagnosis of ovarian cancer and minor illnesses were acceptable (eg common cold, headache). The rest of the criteria (2-3) were identical to that of the cases. In total 48 patients were involved in the study along with 48 healthy controls.

Blood samples were collected in a vacutainer tube containing ethylenediaminetetraacetic acid (EDTA). Genomic DNA and RNA were extracted from the whole blood using DNA and RNA purification kits (*Qiagen*, USA). DNA and RNA concentrations were measured using the fluorometer-based method (*Qubit, Thermo Scientific*, USA).

Genotyping

SNP genotyping was performed using TaqMan assay (*Thermo Scientific*, USA). The selected SNP was rs1800896 SNP upstream of IL-10 gene (IL-10-1082). Each TaqMan SNP genotyping assay contained sequence-specific forward and reverse primers to amplify the polymorphic sequence of interest and 2 TaqMan minor groove binder (MGB) probes with nonfluorescent quenchers (NFQ): One VIC-labelled probe to detect allele 1(A) sequence and one FAM-labelled probe to detect allele 2(G) sequence. Real time-PCR was performed based on standard protocols. The reaction mix, including the TaqMan Master Mix (5.00 uL) and the 20X Assay Working Stock (0.50 uL),

CONTENT

totalled 5.50 uL. Together with the DNA sample (4.50 uL), the final reaction volume was 10 uL. PCR conditions for amplification included polymerase activation at 95 °C for 10 min (hold), denaturation at 95 °C for 15 s and annealing/extension at 60 °C for 1 min (cycle 40). The real-time PCR instrument software plots the results of the allelic discrimination data as a plot of allele 1 (VIC dye) versus allele 2 (FAM dye). The allelic discrimination (AD) plot represents each sample well as an individual point on the plot. A typical AD plot shows homozygote clusters, a heterozygote cluster and the no-template controls. The points in each cluster are grouped closely together and each cluster is located well away from the other clusters.

Reverse transcription

The reverse transcription was carried out by using *Thermo Fisher High-Capacity* cDNA reverse transcription kits. The final volume of each reaction well was 20 µL of which 10 µL was contributed by RNA sample and 10 µL was contributed by 2X RT master mix. The 2X RT master mix was prepared as per the protocol which consisted of 2 µL of RT random primers, 1 µL of *Multiscribe transcriptase*, 0.8 µL of dNTP nucleotide mix, 2 µL of RT buffer and 4.2 µL of nuclease free water to fit each well of 20 µL reaction.

After loading, the PCR conditions for reverse transcription included 10 min of incubation period at 25 °C, 120 mins of second stage at 37 °C and 5 min of final step at 85 °C. The obtained cDNA samples were stored at 4 °C for further analysis.

Gene expression

Gene expression assays for IL-10 was performed using TaqMan gene expression assays (*Thermo Scientific*, USA). The final volume of PCR reaction of each well was 20 µL which contained 1 µL of gene expression assay, 10 µL of gene expression master mix, 4 µL of cDNA template and 5 µL of nuclease free water. The PCR settings for amplification required polymerase activation at 95 °C for 10 min (hold), denaturation at 95 °C for 15 s and annealing/extension at 60 °C for 1 min (cycle 40).

Statistics

The study and control groups were analysed separately. All statistical analyses were performed by GraphPad Prism 9.3.1 for Mac (*GraphPad Software*, San Diego, California USA).

Statistical significance for differences in genotype frequencies was determined by Chi-square and Fisher's exact test and the level of significance was put at $p < 0.05$. An unpaired t-test was used to compare the difference in mean proliferative activity of patients with A/A genotype and patients having the G allele (A/G and G/G). To evaluate associations between the SNPs and the risk of cancer odds ratios (ORs) and 95 % confidence intervals (CIs) were calculated using unconditional logistic regression analysis.

Results

Association between promoter polymorphisms of IL-10 gene and ovarian cancer

The genotype distributions of IL-10 gene polymorphisms among cancer and control groups were all according to the expected Hardy–Weinberg equilibrium. IL-10 (– 1082) allele and genotype distributions of both ovarian cancer patients and controls are illustrated in Table 1. There was no statistically significant difference in frequency of genotypes and alleles between the two groups ($p > 0.05$).

Relationship between IL 10 (– 1082) SNP and expression levels of IL-10 in ovarian cancer

In another analysis, the ovarian cancer samples and controls were grouped according genotypes to the polymorphic variant IL 10 (– 1082) A/A, A/G and G/G. Subjects having the homozygous variant (A/A) had lower IL-10 mRNA levels than those with the homozygous wild (G/G) genotype in both, ovarian cancer patients and controls, $p < 0.05$. In addition, mRNA levels on IL-10 were different among cases and controls ($p < 0.05$). Patients with ovarian cancer had higher level of mRNA for IL-10 in all three groups (Figure 1).

CONTENT

Table 1: Distribution of IL-10 -1082 A/G genotype and allele frequency in ovarian cancer patients and controls

Genotypes or alleles	Cases N (%)	Controls N (%)	OR (95 % CI)	p-value
A/A	11 (22.9 %)	14 (29.2 %)	1.00 (ref)	
A/G	28 (58.3 %)	27 (56.2 %)	1.06 (0.57-1.74)	0.835
G/G	9 (18.8 %)	7 (14.6 %)	0.84 (0.38-2.36)	0.648
A allele	50 (52.1 %)	55 (57.3 %)	1.00 (ref)	
G allele	46 (47.9 %)	41 (42.7 %)	0.46 (0.21-1.43)	0.461

OR: odds ratio; CI: confidence interval;

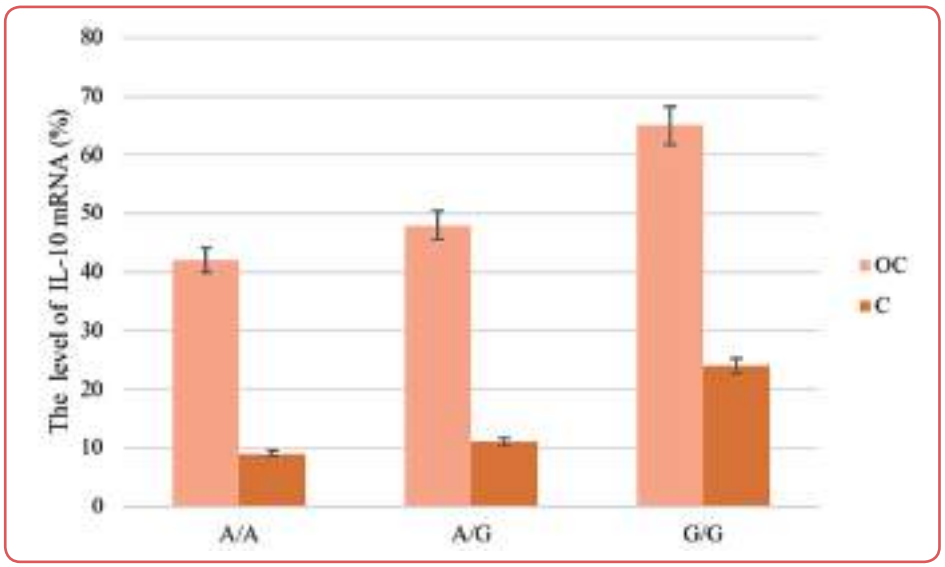


Figure 1: Relative gene expression levels of the IL-10 in the ovarian cancer and control groups
OC: ovarian cancer patients group; C: control group;

Discussion

Cytokines involved in ovarian carcinoma play very important role in survival rate, prognosis, progression free survival and probability of metastasis. Higher concentration of IL-10 protein leads to higher chances of ascites in ovarian cancer patients.[7] As ovarian carcinoma has a very high tendency to metastasise through transcoelomic spread, presence of ascites makes the prognosis even worse as cytokines and chemokines of malignant ascites enhance weakening of cellular tight junctions, transmesothelial migration and epithelial-to-mesenchymal transition.[12] This process fastens the tumour cell seeding throughout the abdominal cavity and promotes tumour growth, thereby reducing the efficiency of debulking surgeries.

The paradox is that IL-10 also plays a crucial role in tumour suppression. IL-10 can suppress HLA expression on the tumour cell surface which activates NK cells against those tumour cells.[6] Another study showed that PEGylated IL-10 activates systemic immunity by $CD8^+$ T cell invigoration, polyclonal T cell expansion; increase the levels of INF-γ, granzyme B in cancer patients and promotes tumour cell regression.[13] There are various trials and studies which showed various modified IL-10 such as, PEG IL-10, PVC-Ag coated IL-10, adenoviral-mediated expression of IL-10 have showed results favouring anti-tumour properties of IL-10.[14]

Presented study showed no clinical significance of IL-10 SNP variant (– 1082) when it comes to G/G vs A/G*A/A polymorphisms. It reflects the results described earlier.[11] Analysis was also ex-

CONTENT

tended with IL-10 expression. This showed that homozygous variant (A/A) had lower IL-10 mRNA levels than those with the homozygous wild (G/G) genotype in both, ovarian cancer patients and controls, ($p < 0.05$). Further analysis showed that patients with ovarian cancer had higher level of mRNA for IL-10.[15]

Furthermore, a study among colorectal cancer patients revealed that the GG genotype of -1082A/G polymorphism in IL-10 were higher in controls compared to colorectal cancer patients.[16] A case control study showed that similar results among breast cancer patients by proving AA genotype shows increased risks towards the development of the breast cancer.[17] While this SNP and corresponding gene expression have been analysed in a number of articles for separately separate groups of population, more studies are needed of rs1800896 SNP of IL-10 gene and IL-10 gene expression in ovarian cancer patients.

IL-10 along with other cytokines play an important role in inducing the immunosuppressive TME. Induced or adapted subset of regulatory T cells (Treg) and tumour cells produce immunosuppressive cytokines such as IL-10, TGF-B, etc. IL-10 in turn makes dendritic cells (DC) dysfunctional which further provides the positive feedback loop to induce and expand Treg cells further by stimulating their proliferation. Treg cells are known to induce tumour specific tolerance and immunosuppression.[5] The IL-10 treated DCs demonstrated antigen specific anergic conditions in both $CD4^+$ and $CD8^+$ T cells as well.[18] But, IL-10 is also believed to be acting with anti tumourogenic properties.

Attempts were made to analyse both rs1800896 SNP of IL-10 gene and IL-10 gene expression in the same group of population. Yet, presented study has some limitations, one of which is the smaller sample size. Seeing some tendency despite this relatively small number of studied cases increases the value of the results and demonstrates importance of further research in this direction. Another significant improvement to study results could be brought by excluding the possibility of other polymorphism in the IL-10 promoter region influencing the gene expression.

Conclusion

Presented results support the theory that IL-10 gene expression levels differ in patients with and without ovarian cancer. Polymorphic variant IL-10 (– 1082) A/G couldn't be confirmed to explain this difference in gene expression levels.

Ethics

The study was approved by the Ethics Committee of Tbilisi State Medical University, Tbilisi, Georgia (decision No N7-2021/91, dated 6 October 2021). Signed informed consent was collected from each of the study participants.

Acknowledgement

The authors are grateful to the participants who took part in the study.

Conflicts of interest

The authors declare that there is no conflict of interest.

Funding

This work was supported by the Shota Rustaveli National Science Foundation of Georgia, Grant YS-21-1216.

Data access

The data that support the findings of this study are available from the corresponding author upon reasonable individual request.

CONTENT

Author ORCID numbers

Pavithra Balakrishnan (PB):
0000-0002-7718-6769
Jahnvi Shah (JS):
0000-0003-4373-4402
Sandro Surmava (SS):
0009-0006-1446-0990
Eka Kvaratskhelia (EK):
0000-0002-1200-0230
Elene Abzianidze (EA):
0000-0002-1140-7688
Nino Vardiashvili (NV):
0009-0005-0047-1253
Ketevani Kankava (KK):
0000-0001-6944-971X

Author contributions

Conceptualisation: PB, EK
Methodology: PB, JS, SS, EK
Validation: SS
Formal analysis: NV
Investigation: PB, JS, SS, EK
Resources: JS, NV
Data curation: SS
Writing - original draft: PB
Writing - review and editing: EK, EA, KK
Supervision: KK
Project administration: EK, EA
Funding acquisition: KK

References

1. Huang J, Chan WC, Ngai CH, Lok V, Zhang L, Lucero-Prisno DE 3rd, et al. On behalf of NCD Global Health Research Group of Association of Pacific Rim Universities Apru. Worldwide burden, risk factors, and temporal trends of ovarian cancer: a global study. Cancers (Basel). 2022 Apr 29;14(9):2230. doi: 10.3390/cancers14092230.
2. Ovarian cancer statistics: World cancer research fund international (2022) WCRF International. [Internet]. [Accessed: 22-Feb-2023]. Available at: https://www.wcrf.org/cancer-trends/ovarian-cancer-statistics/.
3. Guo T, Dong X, Xie S, Zhang L, Zeng P, Zhang L. Cellular mechanism of gene mutations and potential therapeutic targets in ovarian cancer. Cancer Manag Res. 2021 Apr 8;13:3081-100. doi: 10.2147/CMAR.S292992.
4. Surmava S, Kvaratskhelia E, Balakrishnan P, Shah J, Abzianidze E, Tavartkiladze AA, et al. Single nucleotide polymorphisms in the folate metabolic pathway genes and global DNA methylation in ovarian cancer. ESMO Open. 2023; 8(5):101881. doi: 10.1016/j.esmoop.2023.102201.
5. Ning F, Cole CB, Annunziata CM. Driving immune responses in the ovarian tumor microenvironment. Front Oncol. 2021 Jan 15;10:604084. doi: 10.3389/fonc.2020.604084.
6. Mannino MH, Zhu Z, Xiao H, Bai Q, Wakefield MR, FangY. The paradoxical role of IL-10 in immunity and cancer. Cancer Lett. 2015 Oct 28;367(2):103-7. doi: 10.1016/j.canlet.2015.07.009.
7. Mustea A, Könsgen D, Braicu EI, Pirvulescu C, Sun P, Sofroni D, Lichtenegger W, Sehouli J. Expression of IL-10 in patients with ovarian carcinoma. Anticancer Res. 2006 Mar-Apr;26(2C):1715-8. PMID: 16617566.
8. Pisa P, Halapi E, Pisa EK, Gerdin E, Hising C, Bucht A, et al. Selective expression of interleukin 10, interferon gamma, and granulocyte-macrophage colony-stimulating factor in ovarian cancer biopsies. Proc Natl Acad Sci U S A. 1992 Aug 15;89(16):7708-12. doi: 10.1073/pnas.89.16.7708.
9. Zhao S, Wu D, Wu P, Wang Z, Huang J. Serum IL-10 predicts worse outcome in cancer patients: a meta-analysis. PLoS One. 2015 Oct 6;10(10):e0139598. doi: 10.1371/journal.pone.0139598.
10. Lane D, Matte I, Garde-Granger P, Bessette P, Piché A. Ascites IL-10 promotes ovarian cancer cell migration. Cancer Microenviron. 2018 Dec;11(2-3):115-24. doi: 10.1007/s12307-018-0215-3.
11. Ioana Braicu E, Mustea A, Toliat MR, Pirvulescu C, Könsgen D, Sun P, et al. Polymorphism of IL-1alpha, IL-1beta and IL-10 in patients with advanced ovarian cancer: results of a prospective study with 147 patients. Gynecol Oncol. 2007 Mar;104(3):680-5. doi: 10.1016/j.ygyno.2006.10.014.
12. Ford CE, Werner B, Hacker NF, Warton K. The untapped potential of ascites in ovarian cancer research and treatment. Br J Cancer. 2020 Jul;123(1):9-16. doi: 10.1038/s41416-020-0875-x.
13. Naing A, Infante JR, Papadopoulos KP, Chan IH, Shen C, Ratti NP, et al. PEGylated IL-10 (Pegilodecakin) induces systemic immune activation, CD8+ t cell invigoration and polyclonal T cell expansion in cancer patients. Cancer Cell. 2018 Nov 12;34(5):775-791.e3. doi: 10.1016/j.ccell.2018.10.007.
14. Rallis KS, Corrigan AE, Dadah H, George AM, Keshwara SM, Sideris M, et al. Cytokine-based cancer immunotherapy: challenges and opportunities for IL-10. Anticancer Res. 2021 Jul;41(7):3247-52. doi: 10.21873/anticanres.15110.
15. Zhu Z, Liu JB, Liu X, Qian L. Association of interleukin 10 rs1800896 polymorphism with susceptibility to breast cancer: a meta-analysis. J Int Med Res. 2020 Apr;48(4):300060520904863. doi: 10.1177/0300060520904863.

CONTENT

16. Miteva LD, Stanilov NS, Deliysky TS, Stanilova SA. Significance of -1082A/G polymorphism of IL10 gene for progression of colorectal cancer and IL-10 expression. Tumour Biol. 2014 Dec;35(12):12655-64. doi: 10.1007/s13277-014-2589-2.
17. Ahmadi S, Surmava S, Kvaratskhelia E, Abzianidze E, Kankava K. IL-10 polymorphism and breast cancer risk in Georgian women: a case-control study. Glob Med Genet. 2023 Jul 10;10(3):159-63. doi: 10.1055/s-0043-1770957.
18. Yigit R, Massuger LF, Figdor CG, Torensma R. Ovariancancer creates a suppressive microenvironmentto escape immune elimination. Gynecol Oncol. 2010May;117(2):366-72. doi: 10.1016/j.ygyno.2010.01.019.

CONTENT

Khalaf et al. Scr Med. 2024 Mar-Apr;55(2):165-71. DOI:10.5937/scriptamed55-49053

ORIGINAL ARTICLE

Eruption of First Permanent Molar Among a Group of Iraqi Children in Relation to Nutritional Status

Muna Saleem Khalaf,[1] Meena Osama Abdul-Wadood,[1] Asmaa Mohammed Khammas[1]

1. Pedodontics and Preventive Dentistry Department, College of Dentistry, University of Baghdad, Baghdad, Iraq.

Citation:
Khalaf MS, Abdul-Wadood MO, Khammas AM. Eruption of first permanent molar among a group of Iraqi children in relation to nutritional status. Scr Med. 2024 Mar-Apr;55(2):165-71.

Corresponding author:
MUNA SALEEM KHALAF
E: muna.s.khalaf@codental.oubaghdad.edu.iq

Abstract

Background/Aim: The timing of a tooth's eruption can be affected by a variety of factors. The nutritional status has an impact on the development of a child's body. The purpose of the study was to analyse the number of children aged 6 to 9 in an Iraqi Arab population who had erupted permanent first molars and to examine how nutritional status affected the timing and level of emergence.
Methods: A total of 330 boys and girls, in first grade elementary school, made up the sample. First molars that had erupted were noted, along with the level of the eruption. Each child's nutritional status was evaluated by recording their height and weight and body mass index (BMI) value was compared to the 2007 WHO reference.
Results: Girls had higher number of erupted molars than boys did and a correlation between the number of erupted teeth and nutritional condition existed, with a higher mean number of erupted molars in obese children.
Conclusion: BMI had an impact on the timing of the eruption of permanent first molars, a result that was primarily observed in females.

Key words: Body mass index; Eruption time; Stage of eruption; First permanent molars.

Received: 2 February 2024
Revision received: 3 March 2024
Accepted: 3 March 2024

Introduction

Tooth eruption refers to the movement or change in the position of the tooth from the depth of the alveolar bone until it reaches occlusal contact with an opposing and adjoining tooth. When the crown of a tooth has formed completely the tooth will the start its eruptive movement. The eruption of a tooth is completed after about five years from the time the crown formation is completed.[1]

The nutritional status of an individual can be reflected by the status of the oral cavity. Many factors that relate oral health conditions, nutritional status and the general well-being have been found. These include forces exerted by the vascular tissues surrounding and beneath the root, hormonal influences, the presence of a healthy dental follicle, pressure from muscular action, resorption of the alveolar crest, growth and development of the alveolar bone and growth and development of the periodontal membrane.[2]

Delay tooth eruption is applied when the appearance of a tooth in the oral cavity at a time that differs from norms set for various races, ethnicities and sexes. It could be caused by local factors or other factors. Gender, genetics, nutrition, socioeconomic situation and others are a few of the factors that might also delay or impact the eruption of teeth.[3]

Nutrition refers to nutrients that the body utilises to continue in development, maintenance and repair. These substances are provided from food. Anthropometric measurements include many

Copyright © 2024 Khalaf et al. This is an open access article distributed under the Creative Commons Attribution License (CC BY), which permits unrestricted use, distribution and reproduction in any medium, provided the original work is properly cited.

methods that have been used to evaluate nutritional status and provide knowledge on growth and body composition. For the estimation of underweight, stunting, wasting, or overweight associated with a higher likelihood of having adverse health effects, it is crucial to collect such information.[4] Body mass index (BMI) is a metric that has been utilised in dentistry, particularly in research on the relation of obesity to dental caries. It can be calculated counting the square root of a person's weight to height.[5]

Several studies were conducted in Iraq investigating the nutritional status in relation to various variable.[6-10] Few were found that investigated the teeth eruption status. In 2008, Gatta et al clarified that tooth emergence is a process of growth and therefore is related with other body processes, especially child's weight and height.[11] In 2013, Hanoon et al discovered that malnourished children had less permanent teeth erupted in the oral cavity than children, who by height and weight, were defined as well nourished.[12] In 2016, Ahmed and Al-Dahan[13] indicated that Iraqi children showed differences in permanent tooth eruption in comparison with studies carried previous to their study. They stated that the malnutrition children and adolescents showed late eruption of teeth while in 2023, Hassan et al[14] described different results in that the timing if eruption was not related to the feeding pattern nor the level of growth hormone in saliva. Although their study was on primary teeth eruption. Also, results seen by Salim et al[15] revealed that obese individuals and overweight individuals showed eruption of permanent teeth to be delayed in comparison to normal weighing individuals.

These differences in results of previous studies, especially those carried out in Iraqi populations, have provoked the purpose of this study to count the number of permanent first molar teeth that had erupted in a sample of Iraqi children aged 6 to 9 and to assess the impact of nutritional status on the timing and level of those teeth's eruptions.

Methods

The sample size was calculated to be 330 children (164 females and 166 males) using G power 3.0.10. The participating children ranged in age from 6 to 9, Iraqi Arabs and resided in Baghdad. The Scientific Committee and the Central Ethical Committee of the College of Dentistry at the University gave approval for this study. Parents of the children accepted to participate in this study were informed and provided their written consent.

Examination of teeth

The examination was started by recording the determined permanent teeth erupted in the oral cavity. Then the level of eruption of permanent first molars was evaluated while children were standing and under the natural sunlight. Examination of teeth was carried out by the use of a disposable dental mirror. The level of the eruption was measured according to the criteria presented by Carvalho et al.[16]

Criteria for the stage of a permanent first molar's eruption: Stage 0: Not erupted; Stage 1: Partially erupted occlusal surface; Stage 2: Fully erupted occlusal surface with less than 1/2 of crown erupted; Stage 3: Fully erupted occlusal surface with more than 1/2 of crown erupted; Stage 4: Full occlusion.

Measurement of BMI

A computerised weighing scale was used to determine the child's weight. A regular measuring tape that was mounted on the wall was used to measure height. After taking off their shoes, the youngster was instructed to stand up against the measuring tape with their feet parallel to one another. The BMI was calculated as individual's weight in kg divided by the square of their height in m.

The height-for-age (HAZ), weight-for-height (WHZ) and BMI indicator's value was compared to the 2007 WHO reference, chart for ages 5-18 years (z-scores). Four categories were defined: underweight (thinness and severe thinness were appointed to this category), normal weight, overweight and obese.[17]

Statistical analysis

Data were entered into Microsoft Excel and IBM SPSS Statistics version 26 was used for analysis. Normality was assessed using the Shapiro-Wilk test and significant differences were found if $p < 0.05$ between BMI groups.

CONTENT

Results

A total of 164 girls and 166 boys (aged 6-9 years) were recruited in this study. Among the 330 children assessed, 22 (6.67 %) were underweight, 230 (69.69 %) were normal weight, 60 (18.18 %) were overweight and 18 (5.45 %) were obese. The association between gender and BMI was significantly different ($p < 0.05$). Girls were more often overweight and obese (38 and 10, respectively) while boys were more often underweight and normal weight (16 and 120, respectively) as seen in Figure 1.

Girls showed higher mean values (2.45 ± 0.963) for the molar eruption stage than boys (2.18 ± 1.174) and a t-test ($t = 2.223$) revealed that this difference was statistically significant ($p = 0.027$). Using Spearman correlation test, weak positive ($p = 0.002$) correlation was found between the stage of tooth eruption and the nutritional status.

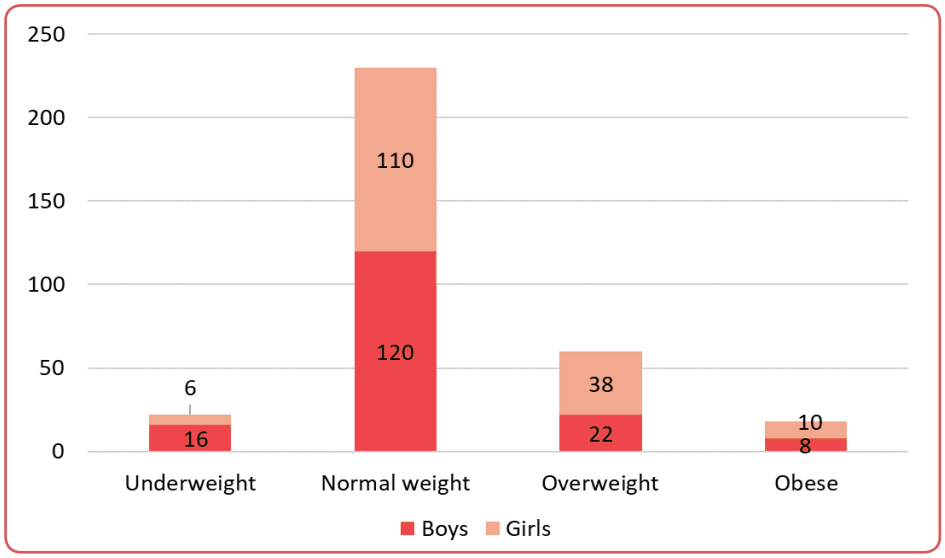


Figure 1: Distribution of the sample according to body mass index (BMI) and gender

A significant difference was found when comparing the number of erupted teeth to the BMI categories using the independent-samples Kruskal-Wallis test ($p = 0.044$). Using pairwise tests the difference was found between the normal and the obese as seen in Table 1 with the highest mean of the erupted molar in obese children.

There was no distinction between the left and right sides. Children who were underweight were shown to have a first molar eruption that was later than the other. The average age and median age at which mandibular and maxillary first molars erupted by BMI categories is shown in Table 2.

Statistically, no significant difference was found in the eruption age between the mandibular and maxillary molar ($t = -0.228$, $p = 0.819$) using t-test. According to the age of the child, underweight

Table 1: Pairwise comparison of the number of erupted teeth and body mass index (BMI) groups

BMI groups	X^2	SE	p-value
Normal-Underweight	14.563	15.360	0.343
Normal-Overweight	-15.151	9.978	0.129
Normal-Obese	-42.017	16.846	0.013*
Underweight-Overweight	-0.588	17.155	0.973
Underweight-Obese	-27.455	21.875	0.209
Overweight-Obese	-26.867	18.497	0.146

**Significant at $p < 0.05$; X^2 = Kruskal-Wallis test; SE: standard error;*

Table 2: Mean age of eruption of molars between body mass index (BMI) groups

BMI groups	Maxillary permanent first molar (Age)		Mandibular permanent first molar (Age)	
	Mean ± SD	Median (IQR)	Mean ± SD	Median (IQR)
Underweight	7.9 ± 1.26	9.0 (2.0)	8.3 ± 0.96	9.0 (2.0)
Normal	7.3 ± 0.96	7.1 (1.3)	7.3 ± 0.96	7.1 (1.3)
Overweight	7.3 ± 1.00	7.1 (1.2)	7.3 ± 0.96	7.1 (1.2)
Obese	6.7 ± 0.36	7.0 (0.4)	6.7 ± 0.36	7.0 (0.4)

SD: standard deviation; IQR: interquartile range;

CONTENT

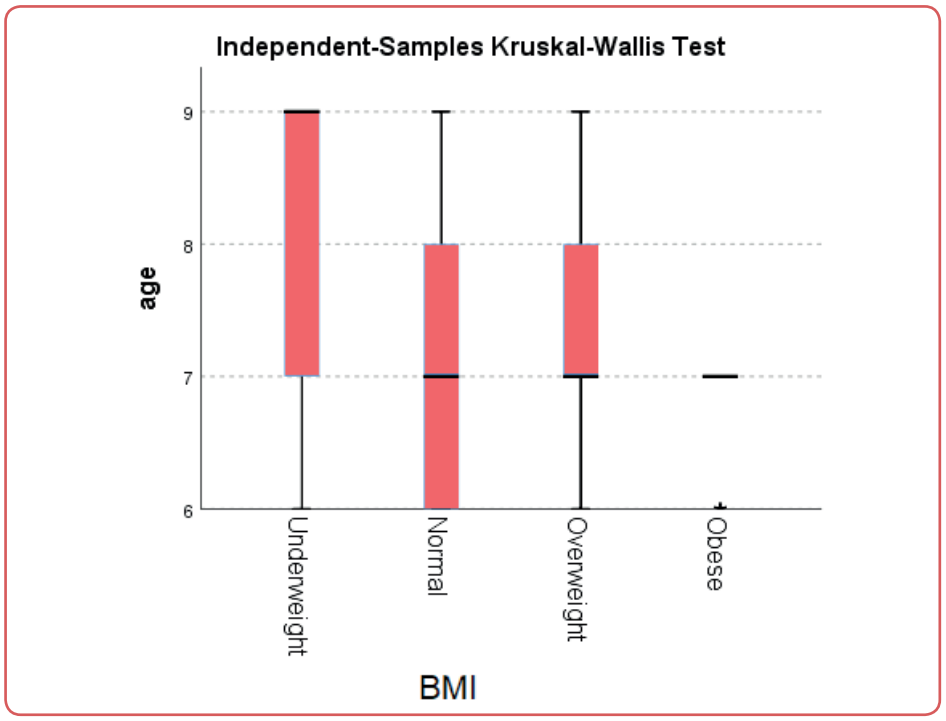


Figure 2: Distribution of the sample according to body mass index (BMI) groups and age

children mostly were at nine years old children (n = 12) while the normal category was mainly 6-7 years old children (n = 78 and 76, respectively). The overweight and obese categories were at seven years old (n = 26 and 14, respectively) as seen in Figure 2. When comparing the nutritional status between the age groups significant difference was found (p = 0.011). Using pairwise tests the differences were found between the underweight and the other categories (Table 3).

Table 3: Comparison of age differences in body mass index (BMI) groups

BMI groups	X^2	SE	p-value
Obese-Normal	23.197	22.307	0.298
Obese-Overweight	38.100	24.493	0.120
Obese-Underweight	83.576	28.966	0.004*
Normal-Overweight	-14.903	13.212	0.259
Normal-Underweight	60.379	20.339	0.003*
Overweight-Underweight	45.476	22.716	0.045*

*SD: standard deviation; IQR: interquartile range; *Significant at $p < 0.05$; X^2 = Kruskal-Wallis test; SE: standard error;*

According to height for age z-score, children were mostly in normal category and only 9 children were in moderate stunting (3 girls, 6 boys). Significant positive correlation (r = 0.4) between z score for height and the stage of the erupted molar ($p < 0.001$) was found.

Discussion

BMI has been long utilised and depended on to compare the anthropometric values of adults and children. However, it refers to body fatness in children.[18] Due to its effect, studied previously, on child's intelligence, occlusion of primary and permanent teeth, caries risk and the timing of preventative and orthodontic intervention, permanent teeth erupt might be affected by nutritional status.[11, 19, 20] These dental conditions put a heavy financial strain on the medical system. Therefore, research to study the variables affecting the period of permanent tooth eruption is very important for clinical personnel and public health strategies.

There was significant difference in the number of erupted permanent first molars between BMI groups, with a higher mean among obese children. These results support the earlier article of Wong et al.[21] As evident from the results, significant sex differences were seen for BMI status in the total sample. The higher number of overweight or obese children was in girls. This was in contrast to Talwar and Airi,[22] who stated in their research that the malnourished were more in girls than boys. However, their investigation was carried out in areas where malnutrition in children is a problem.

Girls had more erupted first permanent molars than boys. Teeth have been seen to emerge a little earlier in girls than boys.[23] The reason for the earlier eruption is unclear. Although it is thought to be related to the difference in sexual maturation of each sex at a specific age. This difference in this study may be due to the finding that malnutrition was more among boys. This result agreed with that of the study done by Ahmed and Al-Dahan[13] and Laith and Al-Rawi.[24] It disagreed with Reis et al[25] study which stated that girls are more prone to delayed teeth eruption compared to boys.

In this study, the mean age of eruption of first molars was found to have a statistically significant difference between underweight, normal, overweight and obese children who were categorised according to BMI status. This finding agreed with Esan and Schepartz.[26] The result of this study showed children in the underweight category showed delayed eruption patterns while obese children had earlier eruption ages compared with those with lower BMI status. Similar observations were made by Reis et al[25] who demonstrated that underweight children had more than 4 times higher chance of presenting delayed teeth eruption. Lack of important nutrients and reduced growth hormones may have been the factor that caused tooth eruption delay in underweight children attributed to altered tooth formation.[27] Since the regulation of the hormones and metabolic processes happens in adipose tissue. Accumulation of adipose tissue leads to hormonal changes in obese individuals, which in turn accelerates the release of growth hormones leading to the eruption of teeth acceleration.[21] A past study revealed dental development was weakly related to nutritional status and maturational status of children when compared to genetic correlates. Genetic correlates are of a reasonable order of magnitude and when studied on monozygotic twin pairs, it was about as high as theory would allow.[28]

The likelihood of developing dental cavities, has also had clinical significance. A tooth that has erupted early will be in the oral cavity and exposed to cariogenic substances for a longer period at a particular age. This in turn will increase the susceptibility of the tooth to develop carious lesions.[29] In order to organise programs that effectively prevent childhood caries, it is important to consider the early tooth eruption in obese children. On the other hand, this was conflicting with Raghavan et al[18] who stated obese children experienced delayed eruption and that the mean age of eruption increased with increasing BMI.

The study was only carried out in a small area of the country. As a result, the results of the current study cannot be extended to the population of Iraq. Further study on nutritional condition and its major impact on delayed tooth eruption is suggested by these findings.

Conclusion

BMI had an impact on the timing of the eruption of permanent first molars, a result that was primarily observed in females.

Ethics

The scientific committee of the Pedodontics and Preventive Dentistry Department and the Central Ethical Committee of the College of Dentistry at the University of Baghdad, Iraq gave approval for this study (Project No 769323, dated 19 January 2023).

Acknowledgement

None.

Conflicts of interest

The authors declare that there is no conflict of interest.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

CONTENT

Data access

The data that support the findings of this study are available from the corresponding author upon reasonable individual request.

Author ORCID numbers

Muna Saleem Khalaf (MSK):
0000-0002-2184-1568
Meena Osama Abdul-Wadood (MOA):
0000-0002-9357-7989
Asmaa Mohammed Khammas (AMK):
0000-0003-3515-5670

Author contributions

Conceptualisation: MSK, MOA, AMK
Methodology: MSK, MOA, AMK
Software: MSK, MOA, AMK
Validation: MSK, MOA, AMK
Formal analysis: MOA, AMK
Investigation: MOA, AMK
Resources: MOA, AMK
Data curation: MOA, AMK
Writing - original draft: MSK
Writing - review and editing: MSK, MOA
Supervision: MSK
Project administration: MSK, MOA, AMK
Funding acquisition: MSK, MOA, AMK

References

1. Demirjian A, Levesque G-Y. Sexual differences in dental development and prediction of emergence. J Dent Res. 1980 Jul;59(7):1110-22. doi: 10.1177/00220345800590070301.
2. Wise G. Cellular and molecular basis of tooth eruption. Orthod Craniofac Res. 2009 May;12(2):67-73. doi: 10.1111/j.1601-6343.2009.01439.x.
3. Suri L, Gagari E, Vastardis H. Delayed tooth eruption: pathogenesis, diagnosis, and treatment. A literature review. Am J Orthod Dentofacial Orthop. 2004 Oct;126(4):432-45. doi: 10.1016/j.ajodo.2003.10.031.
4. World Health Organization. Diet, nutrition, and the prevention of chronic diseases: report of a joint WHO/FAO expert consultation: World Health Organization; 2003. World Health Organ Tech Rep Ser. 2003;916:i-viii, 1-149, backcover. PMID: 12768890.
5. WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet. 2004 Jan 10;363(9403):157-63. doi: 10.1016/S0140-6736(03)15268-3.
6. Al-Ghalebi, S. Oral health status and treatment needs in relation to nutritional status among 9-10 year- old school children in Nassiryia City/Iraq. Master thesis, College of Dentistry, University of Baghdad, 2011.
7. Hasan DM, Hussien BH. Oral health status in relation to nutritional status among kindergarten children aged (4-5) years old in Karbala city / Iraq. Mustansiria Dent J. 2019;14(1):72-9. doi: 10.32828/mdj.v14i1.762.
8. Al-Awadi ZA, Hussien BH. Oral health status in relation to nutritional status among 9 years old school children in Dewanyiah City/Iraq. Mustansiria Dent J. 2017;14(1):80-6. doi: 10.32828/mdj.v14i1.763.
9. AL-Nassary HT, Mohammed AT. Dental caries and treatment needs in relation to nutritional status among kindergartens children in Tikrit City, Iraq. Indian J Public Health Res Dev. 2019 Oct 1;10(10). doi: 10.5958/0976-5506.2019.03095.X.
10. AL Khafaji SY, Al Rawi NA. Oral health in relation to nutritional status among 10 years old primary school children in Al-Hillah city/ Iraq. J Bagh Coll Dent. 2019;31(4):46-50. doi: https://doi.org/10.26477/jbcd.v31i4.2720.
11. Gatta EA, Al-Alousi WS, Diab BS. Primary teeth emergence in relation to nutritional status among 4-48 months old children in Baghdad City. Mustansiria Dent J. 2008;5(1):62-70. doi: doi.org/10.32828/mdj.v5i1.507.
12. Hanoon SA. Effect of protein-energy malnutrition through body mass index on eruption time condition among 6 and 9 years old in primary school children at Sammawa City. J Babylon Univ Appl Sci. 2013;21(06):1-9.
13. Ahmed HS, Al-Dahan ZA. Time of emergence of permanent teeth and impact of nutritional status among 4-15 years old children and teenagers in Bashar City, Iraq. J Baghdad Coll Dent. 2016;325:1-7. doi: 10.12816/0033224.
14. Hassan DHM, Al-Joranii SM. Effect of feeding pattern and salivary level of growth hormone on the stage of primary tooth eruption: an analytical cross-sectional study. Dent Hypotheses. 2023;14:52-4. doi: 10.4103/denthyp.denthyp43_23.
15. Salim Younis M, Ahmed K, Mand W, Hameed Fatah S. The correlation between BMI and dental caries/tooth eruption among 12 years old school children in both private and governmental in Erbil City. Eurasian J Sci Eng. 2023;9(2):1-11. doi: 10.23918/eajse.v9i2p1.
16. Carvalho JC, Ekstrand KR, Thylstrup A. Dental plaque and caries on occlusal surfaces of first permanent molars in relation to stage of eruption. J Dent Res. 1989;68:773-9. doi: 10.1177/00220345890680050401.
17. de Onis M, Onyango AW, Borghi E, Siyam A, Nishida C, Siekmann J. Development of a WHO growth reference for school-aged children and adolescents. Bull World Health Organ. 2007 Sep;85(9):660-7. doi: 10.2471/blt.07.043497.
18. Raghavan A, Srinivasan N, Sherif AS, Somasundaram N, Govindhan M, Diwakar MKP. Association between mean age of eruption of the permanent teeth and body mass index among school-going children of 7–17 years of age in Chennai City. J Oral Health Comm Dent. 2019;13:40. doi: 10.5005/jp-journals-10062-0047.

CONTENT

19. Mohamedhussein N, Busuttil-Naudi A, Mohammed H, UlHaq A. Association of obesity with the eruption of first and second permanent molars in children: a systematic review. Eur Arch Paediatr Dent. 2020 Feb;21(1):13-23. doi: 10.1007/s40368-019-00452-6.
20. Jafar ZJ. Oral health and nutritional status in relation to intelligence quotient (IQ) of children in Baghdad. J Int Dent Med Res. 2019;12:1487-91.
21. Wong HM, Peng S-M, Yang Y, King NM, McGrath CPJ. Tooth eruption and obesity in 12-year-old children. J Dent Sci. 2017;12:126-32. doi: 10.1016/j.jds.2016.10.004.
22. Talwar I, Airi P. Physical growth and nutritional status of children aged 6-8 years of Panchkula city (Haryana), India. Human Biol Rev. 2015;4:1-26.
23. Kutesa A, Nkamba EM, Muwazi L, Buwembo W, Rwenyonyi CM. Weight, height and eruption times of permanent teeth of children aged 4–15 years in Kampala, Uganda. BMC Oral Health. 2013;13:1-8. doi: 10.1186/1472-6831-13-15.
24. Laith NMH, Al-Rawi NA. Dentition status in relation to nutritional condition among a group of intermediate school students in Al-Najaf city/Iraq. J Baghdad Coll Dent. 2017;29:89-95. doi: 10.12816/0043003.
25. Reis CL, Barbosa MC, Henklein S, Madalena IR, de Lima DC, Oliveira MA, et al. Nutritional status is associated with permanent tooth eruption in a group of Brazilian school children. Glob Pediatr Health. 2021;8:2333794X211034088. doi: 10.1177/2333794X211034088.
26. Esan TA, Schepartz LA. Does nutrition have an effect on the timing of tooth formation? Am J Phys Anthropol. 2020 Mar;171(3):470-80. doi: 10.1002/ajpa.23987.
27. Hegde RJ, Vadgaonkar V, Kamath S. A correlative analysis of dental age, chronological age, and body mass index and its impact on dental development in 6-13 year old children of Navi Mumbai, India. J Indian Soc Pedod Prev Dent. 2018 Oct-Dec;36(4):376-80. doi: 10.4103/JISPPD.JISPPD_189_18.
28. Garn SM, Lewis AB, Kerewsky RS. Genetic, nutritional, and maturational correlates of dental development. J Dent Res. 1965;44:228. doi: 10.1177/00220345650440011901.
29. Peng SM, Wong HM, King NM, McGrath C. Association between dental caries and adiposity status (general, central, and peripheral adiposity) in 12-year-old children. Caries Res. 2014;48(1):32-8. doi: 10.1159/000351690.

CONTENT

Pawestri et al. Scr Med. 2024 Mar-Apr;55(2):173-9. DOI:10.5937/scriptamed55-47262

ORIGINAL ARTICLE

Effectiveness of Progressive Muscle Relaxation Compared to BL 23 and GV 3 Point Acupressure Therapy in Reducing Back Pain Intensity in Third Trimester Pregnant Women

Pawestri Pawestri,[1, 2] Esti Yunitasari,[1] Nikmatul Khayati,[2] Satriya Pranata[2]

1. Faculty of Nursing, Universitas Airlangga, Surabaya, East Java, Indonesia.
2. Faculty of Nursing and Health Sciences, Universitas Muhammadiyah Semarang, Semarang, Central Java, Indonesia.

Citation:
Pawestri P, Yunitasari E, Khayati N, Pranata S. Effectiveness of progressive muscle relaxation compared to BL 23 and GV 3 point acupressure therapy in reducing back pain intensity in third trimester pregnant women. Scr Med. 2024 Mar-Apr;55(2):173-9.

Corresponding author:
PAWESTRI PAWESTRI
E: pawestri@unimus.ac.id

Abstract

Background/Aim: Back pain is one of the most common discomforts experienced by pregnant women in the third trimester of pregnancy. Interventions that can be done to overcome this are progressive muscle relaxation or acupressure at the BL 23 and GV 3 points. The aim was to determine the effectiveness of progressive muscle relaxation with BL 23 and GV 3 acupressure to reduce low back pain in third trimester pregnant women.
Methods: Quasi-experimental research design method with a two-group pretest and post-test design approach was conducted. The total sample was 88 with inclusion criteria - third trimester pregnant women who experienced back pain. Pain was measured with numerical rating scale (NRS) and analysed using Wilcoxon test.
Results: The average reduction in back pain for pregnant women after progressive muscle relaxation was 2.12, while the average reduction in back pain for pregnant women after BL 23 and GV 3 acupressure was 1.50. There is a mean difference between the two (0.62), so it can be concluded that there was a difference in the effectiveness of reducing back pain for pregnant women in the third trimester between the progressive muscle relaxation intervention and the respondents' pain scale after the acupressure therapy intervention at points BL 23 and GV 3.
Conclusion: Back pain for pregnant women in the third trimester can be treated with progressive muscle relaxation therapy or acupressure at points BL 23 and GV 3 to reduce back pain. Progressive muscle relaxation therapy was more effective. Progressive muscle relaxation can be done by pregnant women themselves when back pain occurs.

Key words: Back pain; Pregnant women; Progressive muscle relaxation; BL 23; GV 3; Acupressure.

Received: 22 October 2023
Revision received: 27 March 2024
Accepted: 27 March 2024

Introduction

During pregnancy, a woman experiences many changes, both physiological and psychological.[1, 2] Physiological changes that occur not only in the reproductive organs but also in the cardiovascular, respiratory, renal, integumentary, musculoskeletal, neurological, digestive and endocrine systems can cause discomfort, especially in the second and third trimesters.[3] Physical changes

Copyright © 2024 Pawestri et al. This is an open access article distributed under the Creative Commons Attribution License (CC BY), which permits unrestricted use, distribution and reproduction in any medium, provided the original work is properly cited.

CONTENT

can include dyspnoea, insomnia, gingivitis and expulsion, frequent urination, pressure and discomfort in the perineum, back pain, constipation, varicose veins, fatigue, Braxton Hicks contractions, leg cramps, ankle oedema.[4, 5] One of the problems faced by pregnant women in the third trimester is back pain. Back pain can appear at the beginning of the trimester and then peak in the third and second trimesters.[6]

Back pain is one of the most common discomforts experienced by pregnant women in the third trimester of pregnancy.[6] Based on research conducted on pregnant women, it shows that the prevalence of back pain in pregnant women is 70-86 %.[7] The study mentions that the prevalence of back pain in third trimester pregnant women was 33.7 %.[8] According to the study, 73.33 % of pregnant women experienced moderate pain, while 16.67 % experienced severe pain and 10 % experienced mild pain.[9] Based on the Indonesian health data profile, 5,298,285 pregnant women were experiencing back pain in Indonesia, in the Central Java province the number was 314,492, in the Semarang City area 53,734 pregnant women experienced back pain.[10] Back pain that occurs during pregnancy occurs due to anatomical changes in the body. Back pain is the most commonly reported complaint of pregnant women.[7–9]

The impact of back pain complaints on pregnant women in the third trimester is that mothers feel uncomfortable with their activities or have disturbed activities, are anxious, experience changes in the shape of their body structure and experience long-term back pain, thereby increasing the tendency for back pain.[11] Pain causes pregnant women to experience fear and anxiety, thereby increasing stress and experiencing physiological changes during pregnancy.[12] Pain and anxiety are synergistic and exacerbate each other, a sign of discomfort in pregnant women experiencing pain in the back.[7] Back pain causes a person to experience fear and anxiety, resulting in stress during pregnancy, which has an impact on the pregnancy process. Back pain in pregnant women has the impact that a pregnant woman will feel fear and anxiety, thereby increasing stress and experiencing physiological changes.[13] Around 75-90 % of back pain in pregnancy affects the level of quality of life, limits activity and productivity and even creates physical disabilities in pregnant women.[7, 14]

Therapies that can be used to reduce back pain for pregnant women in the third trimester include progressive muscle relaxation, BL 23 and GV 3 acupressure.[15–17] Progressive muscle relaxation therapy is carried out by tightening and relaxing the muscles at one time to provide a feeling of physical relaxation.[18, 19] Progressive muscle relaxation therapy can also be done by stretching and relaxing each group of muscles at the same time which will produce progressive relaxation of the entire body, as well as calming the mind by stretching for three to five seconds and focusing attention.[7, 19] Progressive muscle relaxation is one of the complementary therapies that nurses can use as a non-pharmacological therapy. Progressive muscle relaxation can be given to pregnant women who experience sleep disturbances, back pain, anxiety and stress the benefits of progressive muscle relaxation therapy can provide a feeling of relaxation and calm, improve blood flow and reduce muscle tension.[18–20] One non-pharmacological treatment method for dealing with back pain in third trimester pregnant women is the progressive muscle relaxation technique which is carried out to reduce the intensity of back pain.[21]

With acupressure therapy at points, BL 23 and GV 3, based on the study, point GV 3 shows that acupressure influences reducing the level of back pain in pregnant women.[15, 22] Acupressure measures to treat back pain at the Shenshu point, bladder point (BL 23) can facilitate blood flow located in the lumbar area on the same inferior line as the second lumbar spine spinous process, point (GV 3) can facilitate blood flow which is located between the third and fourth lumbar.[17, 22, 23] There is a decrease in the intensity of back pain in pregnant women in the third trimester after performing acupressure at BL 23, which means that there is an influence of acupressure at BL 23 on the intensity of lower back pain in pregnant women in the third trimester.[15, 22, 24] Thus, this study aimed to determine the difference in back pain intensity of pregnant women in the third trimester who underwent progressive muscle relaxation therapy and acupressure therapy at points BL 23 and GV 3.

CONTENT

Methods

The research design was carried out as a quasi-experiment with a two-group pretest and post-test design approach. The research was conducted at the Semarang City Maternity Clinic, Indonesia.

The number of respondents was 88 divided into two groups, 44 respondents underwent progressive muscle relaxation intervention and other 44 respondents underwent acupressure therapy intervention at points BL 23 and GV 3. Including criteria was: pregnant women in the third trimester who experienced back pain, older than 20 and younger than 35 years of age, gestational age more than 28 weeks and willingness to participate.

Interventions

The researcher delivered a questionnaire before the intervention (pretest) and examined the completeness of filling out the questionnaire. The intervention stage was carried out by progressive muscle relaxation therapy and acupressure therapy at points BL 23 and GV 3 on each respondent with a prospective random sampling design. The final stage was to review the intensity of back pain by using a pain scale instrument called the numeric rating scale (NRS).[25]

Statistical and data analysis

Univariate analysis was carried out on the variable intensity of back pain in third trimester pregnant women. Bivariate analysis was carried out to analyse differences in the effectiveness of reducing the intensity of back pain in third trimester pregnant women who underwent progressive muscle relaxation intervention and acupressure therapy at points BL 23 and GV 3. Bivariate analysis used the Wilcoxon test because the data was non-parametric with non-normal data distribution.

Results

The number of respondents was 88, 44 of third trimester pregnant women underwent progressive muscle relaxation intervention and 44 underwent acupressure therapy intervention at points BL 23 and GV 3. Characteristics of respondents is shown in Table 1.

Table 1: Characteristics of third trimester pregnant women with back pain

Parameter	N	%
Age (year)		
20-35	85	96.59
> 35	3	3.41
Gestational age (weeks)		
28-30	21	23.90
31-35	32	36.40
36-40	34	38.60
41-45	1	1.10
Occupation		
Private employee	36	40.90
Housewife	40	45.50
Teacher	5	5.70
Trader	5	5.70
Government employee	2	2.30
Total	**88**	**100.00**

Intensity of back pain of third trimester pregnant women before and after progressive muscle relaxation therapy intervention is shown in Table 2. The back pain scale before the progressive muscle relaxation intervention was a minimum of 5, a maximum of 8 and the average pain scale was 6.05 ± 0.834. After progressive muscle relaxation intervention pain scale was a minimum of 2 and a maximum of 6 and the average pain scale was 3.93 ± 1.065.

Intensity of back pain of third trimester pregnant women before and after acupressure intervention points BL 23 and GV 3 is shown in Table 3. The back pain scale before the acupressure therapy intervention at points BL 23 and GV 3 was a minimum of 4, a maximum of 7 and the average pain scale was 6.25 ± 0.811. Pain scale after acupressure therapy was a minimum of 3 and a maximum of 6 and the average pain scale was 4.75 ± 0.918.

The average reduction in pain intensity in the progressive muscle relaxation intervention was 2.12, while the average reduction in pain inten-

CONTENT

Table 2: Back pain in third trimester pregnant women before and after progressive muscle relaxation (PMR) therapy intervention according to the numerical rating scale (NRS)

NRS	n	Min	Max	Mean	SD	Z	p-value
Back pain before PMR	44	5	8	6.05	0.834	-5.834	< 0.001
Back pain after PMR	44	2	6	3.93	1.065		

n: number of participants; Min: minimum; Max: maximum, SD: standard deviation; Z: Wilcoxon test value;

Table 3: Back pain in third trimester pregnant women before and after acupressure intervention points BL 23 and GV 3 according to the numerical rating scale (NRS)

NRS	n	Min	Max	Mean	SD	Z	p-value
Back pain before acupressure intervention BL 23 and GV 3	44	4	7	6.25	0.811	-5.753	< 0.001
Back pain after acupressure intervention BL 23 and GV 3	44	3	6	4.75	0.918		

n: number of participants; Min: minimum; Max: maximum, SD: standard deviation; Z: Wilcoxon test value;

Table 4: Difference in means of back pain decrease in pregnant women in the 3rd trimester after progressive muscle relaxation intervention compared to acupressure at points BL 23 and GV 3

Research variable	Intervention	Mean	Z	p-value
Intensity scale of back pain for pregnant women in the 3rd trimester	Progressive muscle relaxation	2.12	-5.834	< 0.001
	Acupressure at points BL 23 and GV 3	1.50	-5.753	

sity in the BL 23 and GV 3 acupressure interventions was 1.50. There was an average difference in decrease of 0.62. Reduction of back pain in third trimester pregnant women with progressive motor relaxation intervention was more effective than acupressure therapy at points BL 23 and GV 3 (Wilcoxon test, $p < 0.001$) (Table 4).

Discussion

The research results showed that the age of the respondents was between 20-35 years old (96 %). In this study, data was obtained that the respondents were in the productive age range during pregnancy. The age range of 20-35 years is the ideal age during pregnancy where the reproductive organs develop optimally and psychological development is very good in preparing for pregnancy. The safest age for a woman to get pregnant is 20-35 years old, if the age is above or below this age there is a risk of complications during pregnancy and childbirth.[3, 26] Pregnant women under the age of 20 are at risk of miscarriage, premature birth, anaemia in pregnancy, congenital abnormalities, easy infection, poisoning and death.[27, 28] Ages over 35 years are at risk of complications during pregnancy. The risk of pregnancy complications over the age of 35, where at that age there are changes in the tissues of the uterus and the birth canal is no longer flexible, which can result in high blood pressure, excess weight, diabetes and labour that is more difficult and prolonged are problems that can occur.[29] Other dangers that can occur are pre-eclampsia, premature rupture of membranes, obstructed labour and post-natal bleeding.[30]

The back pain of pregnant women who underwent progressive muscle relaxation experienced a very significant reduction. In line with the study, back pain in third trimester pregnant women can be treated with progressive muscle relaxation therapy.[18, 19] This occurs because back pain occurs due to muscle tension in the back and pelvic muscles, so by carrying out progressive muscle relaxation interventions, the tense muscles begin to relax and loosen. The progressive muscle relaxation technique is a method that can be used to overcome the intensity of back pain in pregnant women.[18] The progressive muscle relaxation technique is a nursing intervention to

CONTENT

reduce back pain in pregnant women that has no side effects, is very easy for pregnant women to do themselves and costs nothing.

Progressive muscle relaxation is a complementary therapy for dealing with back pain in pregnant women that can be given or taught by nurses to clients. The principle of progressive muscle relaxation is to relax the muscles and mind by stretching and relaxing each group of muscles for five seconds and concentrating the mind followed by deep breathing and then releasing tension until the muscles become limp.[21] The effect of progressive muscle relaxation provides a feeling of comfort that stimulates endorphin hormones. An increase in endorphin hormones in the blood can inhibit pain nerve endings and prevent pain stimuli from entering the spinal cord so that the quality of pain is reduced in the cerebral cortex.[31, 32] Movements in progressive muscle relaxation help relax the muscles so that they become relaxed and then back pain can be controlled. Back pain is transmitted by visceral pain impulses originating from the back muscles and pelvic muscles through sensory nerve fibres that run in the sympathetic nerves.[18]

The results of this study showed that the back pain scale of pregnant women in the third trimester of respondents before the acupressure therapy intervention at points BL 23 and GV 3 was a minimum of 4, a maximum of 7, the average pain scale was 6.25. The respondents' pain scale after acupressure therapy intervention at points BL 23 and GV 3 was a minimum of 3 and a maximum of 6, the average pain scale was 4.75. Acupressure is a technique that applies physical pressure to the surface of the body which is a place for energy circulation and balance in cases of pain. For back pain, acupressure intervention at points BL 23 and GV 3 can also reduce back pain in pregnant women.[22–24] When acupressure points are stimulated, there is a release of tension in the muscles or increased blood circulation, relaxing the pelvic muscles. Massaging at BL 23 can reduce back pain in pregnant women in the third trimester.[22] The acupressure technique at points BL 23, GV 3 and GV 4 can effectively reduce back pain in third trimester pregnant women. Acupressure energy at acupuncture points will flow through the meridians to the target organs. Stimulation or sedation of target organs will affect changes in biochemistry, physiology and perception/taste.[16]

The acupressure mechanism contributes to the stimulation of the pituitary-hypothalamus complex, releasing β-endorphins systemically into the bloodstream from the pituitary gland, resulting in the release of β-endorphins accompanied by the release of adrenocorticotropic hormone.[23] Biochemical changes can occur in the form of increased serotonin and endorphin levels, physiological changes can occur in the form of oxygen activity and blood flow and changes in perception/taste can occur in the form of decreased pain levels.[17]

Progressive muscle relaxation is more effective in reducing back pain in the third trimester of pregnant women by the principle of the progressive muscle relaxation movement is a combination of deep breathing relaxation with contraction-relaxation of the muscles, thus causing a pleasant feeling of comfort and relaxation.[21] The effect of progressive muscle relaxation training is that the parasympathetic nerve fibres will be active and activate endorphin hormones which function to get a happy effect and return the body to a normal condition so that the muscles relax and reduce pain, anxiety and stress.[19, 31] A relaxation technique that can reduce tension, is comfortable because it is equipped with deep breathing exercises and a series of movements from the face to the feet so that it can stimulate the release of endorphins hormones and reduce feelings of pain.[31]

In this study, the results showed that progressive muscle relaxation was more effective for dealing with third trimester pregnant women's back pain compared to acupressure at points BL 23 and GV 3. This was because there was an active process from the respondents to carry out muscle relaxing movements coupled with deep breathing relaxation, then also perform muscle movements both on the face, body and legs to increase muscle relaxation; widen blood vessels reduce pain due to spasm or stiffness in the muscles.[19, 31] Progressive muscle relaxation is identifying tense muscles and then reducing tension by carrying out progressive muscle relaxation techniques to get a relaxed feeling so that it can reduce pain.[18, 21] Acupressure at points BL 23 and GV 3 in this study can also reduce back pain for pregnant women in the third trimester, however when compared with progressive muscle relaxation it is less effective.[15, 17, 22] This is because the implementation of acupressure is only carried out once, so the intervention needs to be repeated so that the results will be maximal. The frequency of acupressure therapy performed 2 times is more effective than 1 intervention.[24]

CONTENT

Conclusion

Back pain for pregnant women in the third trimester can be treated with progressive muscle relaxation therapy or acupressure at points BL 23 and GV 3 to reduce back pain. Both therapies can be used to reduce back pain for pregnant women in the third trimester with the right methods and techniques. Progressive muscle relaxation therapy was more effective. Progressive muscle relaxation can be done by pregnant women themselves when back pain occurs.

Ethics

This study was approved by the Health Research Ethics Committee Universitas Muhammadiyah Semarang, Indonesia (decision No 230/KE/09/2023, dated 11 December 2023).

Acknowledgement

We would like to express our gratitude to any parties for support in this study.

Conflicts of interest

The authors declare that there is no conflict of interest.

Funding

We would like to express our thanks to Universitas Muhammadiyah Semarang for funding support.

Data access

The data that support the findings of this study are available from the corresponding author upon reasonable individual request.

Author ORCID numbers

Pawestri Pawestri (PP):
0000-0002-4457-1441
Esti Yunitasari (EY):
0000-0002-6401-0748
Nikmatul Khayati (NK):
0000-0002-9608-2842
Satriya Pranata (SP):
0000-0002-2026-8931

Author contributions

Conceptualisation: PP
Methodology: PP
Validation: EY
Formal analysis: NK
Investigation: SP
Resources: SP
Data curation: PP
Writing - original draft: PP
Writing - review and editing: EY
Visualisation: NK
Supervision: EY
Project administration: SP
Funding acquisition: NK

References

1. Shafaei FS, Mirghafourvand M, Havizari S. The effect of prenatal counseling on breastfeeding self-efficacy and frequency of breastfeeding problems in mothers with previous unsuccessful breastfeeding: A randomized controlled clinical trial. BMC Womens Health. 2020;20(1):1-11. doi:10.1186/s12905-020-00947-1.
2. Azza A, Triharini M. A cultural nursing care model to prevent preeclampsia in the provision of basic services in eastern Indonesia. AJNM. 2023;5293. doi:10.25159/2520-5293/13903.
3. Brand C, Fochesatto CF, Villa-González E, Silveira JFC, Dias AF, Quevedo Alves F, et al. From pregnancy to breastfeeding: adequate maternal body mass index is essential to prevent a high body mass index in your children. J Pediatr Endocrinol Metab. 2022 Jul 11;35(8):1033-40. doi: 10.1515/jpem-2022-0174.
4. Battulga B, Benjamin MR, Chen H, Bat-Enkh E. The impact of social support and pregnancy on subjective well-being: a systematic review. Front Psychol. 2021;12:710858. doi:10.3389/fpsyg.2021.710858.
5. Lagadec N, Steinecker M, Kapassi A, Magnier AM, Chastang J, Robert S, et al. Factors influencing the quality of life of pregnant women: a systematic review. BMC Pregnancy Childbirth. 2018 Nov 23;18(1):455. doi: 10.1186/s12884-018-2087-4.
6. Ho SSM, Yu WWM, Lao TT, Chow DHK, Chung JWY, Li Y. Garment needs of pregnant women based

CONTENT

on content analysis of in-depth interviews. J Clin Nurs. 2009;18(17):2426-35. doi:10.1111/j.1365-2702.2009.02786.x.
7. Mueller SM, Grunwald M. Effects, side effects and contraindications of relaxation massage during pregnancy: a systematic review of randomized controlled trials. J Clin Med. 2021;10(16):3485. doi:10.3390/jcm10163485.
8. Huang L, Li J, Xiao B, Tang Y, Huang J, Li Y, et al. Bibliometric analysis of research trends on manual therapy for low back pain over past 2 decades. J Pain Res. 2023;16:3045-60. doi:10.2147/jpr.s418458.
9. Shirado O, Arai Y, Iguchi T, Imagama S, Kawakami M, Nikaido T, et al. Formulation of Japanese Orthopaedic Association (JOA) clinical practice guideline for the management of low back pain- the revised 2019 edition. J Orthop Sci. 2021;27(1):3-30. doi:10.1016/j.jos.2021.06.024.
10. Kemenkes. Laporan Nasional RISKESDAS. Published 2018.[Internet]. [Cited: 10-Jan-2024] Available at: https://www.litbang.kemkes.go.id/laporan-riset-kesehatan-dasar-riskesdas/. Indonesian.
11. Johnson MI, Paley CA, Wittkopf PG, Mulvey MR, Jones G. Characterising the features of 381 clinical studies evaluating transcutaneous electrical nerve stimulation (TENS) for pain relief: a secondary analysis of the Meta-TENS study to improve future research. Medicina (Kaunas). 2022;58(6):803. doi:10.3390/medicina58060803.
12. Sharpe EE, Rollins MD. Beyond the epidural: Alternatives to neuraxial labor analgesia. Best Pract Res Clin Anaesthesiol. 2022;36(1):37-51. doi:10.1016/j.bpa.2022.04.005.
13. Leutenegger V, Grylka-Baeschlin S, Wieber F, Daly D, Pehlke-Milde J. The effectiveness of skilled breathing and relaxation techniques during antenatal education on maternal and neonatal outcomes: a systematic review. BMC Pregnancy Childbirth. 2022;22(1):856. doi:10.1186/s12884-022-05178-w.
14. Günebakan Ö, Acar M. The effect of tele-yoga training in healthy women on menstrual symptoms, quality of life, anxiety-depression level, body awareness self-esteem during COVID-19 pandemic. Irish J Med Sci (1971 -). 2022;192(1):467-79. doi:10.1007/s11845-022-02985-0.
15. Kafaei-Atrian M, Mirbagher-Ajorpaz N, Sarvieh M, Sadat Z, Asghari-Jafarabadi M, Solhi M. The effect of acupressure at third liver point on the anxiety level in patients with primary dysmenorrhea. Iran J Nurs Midwifery Res. 2016;21(2):142-6. doi:10.4103/1735-9066.178233.
16. Istiqomah SBT, Yani DP, Retnowuni A. Acupressure as an Adjunctive treatment to improve social interaction skills in autistic toddlers in Jombang Regency, Indonesia. Int J Adv Heal Sci Technol. 2022;2(6). doi:10.35882/ijahst.v2i6.197.
17. Sorour AS, Ayoub AS, Abd El Aziz EM. Effectiveness of acupressure versus isometric exercise on pain, stiffness, and physical function in knee osteoarthritis female patients. J Adv Res. 2014;5(2):193-200. doi:10.1016/j.jare.2013.02.003.
18. Izgu N, Metin ZG, Karadas C, Ozdemir L, Metinarikan N, Corapcıoglu D. Progressive muscle relaxation and mindfulness meditation on neuropathic pain, fatigue, and quality of life in patients with type 2 diabetes: a randomized clinical trial. J Nurs Scholarsh. 2020;52(5):476-87. doi:10.1111/jnu.12580.
19. Tan XYJ, Choong SYX, Cheng LJ, Lau Y. Relaxation interventions for improving sleep outcomes in perinatal women: A systematic review and meta-analysis of randomized controlled trials. Midwifery. 2021;103:103151. doi:10.1016/j.midw.2021.103151.
20. Kiyak S, Kocoglu-Tanyer D. Effectiveness of progressive muscle relaxation and laughter therapy on mental health and treatment outcomes in women undergoing in vitro fertilization: A randomized controlled trial. Res Nurs Health. 2021;44(6):945-56. doi:10.1002/nur.22187.
21. Pawestri P, Machmudah M, Rejeki S, Pranata S, Fitria SAN, Fitri ML, et al. Difference effectiveness of progressive muscle relaxation therapy and endorphin massage therapy towards reducing menstrual pain intensity in adolescents. J Res Heal. 2023;13(4):247-54. doi:10.32598/jrh.13.4.2183.1.
22. Yeh CH, Chien LC, Huang LC, Suen LKP. Auricular point acupressure for chronic pain. Holist Nurs Pract. 2014;28(3):184-94. doi:10.1097/hnp.0000000000000027.
23. Mehta P, Dhapte V, Kadam S, Dhapte V. Contemporary acupressure therapy: Adroit cure for painless recovery of therapeutic ailments. J Tradit Complement Med. 2016;7(2):251-63. doi:10.1016/j.jtcme.2016.06.004.
24. Simsek Kucukkelepce D, Unver H, Nacar G, Tashan ST. The effects of acupressure and yoga for coping with premenstrual syndromes on premenstrual symptoms and quality of life. Complement Ther Clin Pract. 2020;42:101282. doi:10.1016/j.ctcp.2020.101282.
25. Lee SY, Kim JB, Lee JW, Woo AM, Kim CJ, Chung MY, et al. A quantitative measure of pain with current perception threshold, pain equivalent current, and quantified pain degree: a retrospective study. J Clin Med. 2023 Aug 23;12(17):5476. doi: 10.3390/jcm12175476.
26. Fu CY, Wang LZ, Tang XJ, Xia F. Association of labor epidural analgesia use with exclusive breastfeeding up to six months: a online-based cross sectional survey in Jiaxing, China. BMC Pregnancy Childbirth. 2022;22(1):973. doi:10.1186/s12884-022-05332-4.
27. Yasuda S, Fukuda T, Toba N, Kamo N, Imaizumi K, Yokochi M, et al. Risk factors for discontinuation of exclusive breast feeding within 1month: a retrospective cohort study in Japan. Int Breastfeed J. 2022;17(1):20. doi:10.1186/s13006-022-00449-w.
28. Siramaneerat I, Agushybana F, Meebunmak Y. Maternal risk factors associated with low birth weight in Indonesia. Open Public Health J. 2018;11(1):376-83. doi:10.2174/1874944501811010376.
29. Osawa E, Kodama T. Regional socio-environmental characteristics associated with inadequate prenatal care during pregnancy: an ecological study of 47 prefectures in Japan. BMC Pregnancy Childbirth. 2021;21(1):619. doi:10.1186/s12884-021-04100-0.
30. Rawlins B, Plotkin M, Rakotovao JP, Getachew A, Vaz M, Ricca J, et al. Screening and management of pre-eclampsia and eclampsia in antenatal and labor and delivery services: Findings from cross-sectional observation studies in six sub-Saharan African countries. BMC Pregnancy Childbirth. 2018;18(1):346. doi:10.1186/s12884-018-1972-1.
31. Chellew K, Evans P, Fornes-Vives J, Pérez G, Garcia-Banda G. The effect of progressive muscle relaxation on daily cortisol secretion. Stress. 2015;18(5):538-44. doi:10.3109/10253890.2015.1053454.
32. Rahmawati PM, Musviro M, Deviantony F. Effectiveness of progressive muscle relaxation (pmr) on reducing blood pressure in hypertension patients. Indones J Heal Sci. 2018;188. doi:10.32528/ijhs.v0i0.1547.

CONTENT

Peixoto et al. Scr Med. 2024 Mar-Apr;55(2):181-6. DOI:10.5937/scriptamed55-48839

ORIGINAL ARTICLE

Prevalence of Vitamin B_{12} Deficiency in Patients Treated With Metformin

Bruno Daniel Oliveira Peixoto,[1] Mariana Abreu Gonçalves,[2] Ana Isabel Ferreira da Costa,[1] Teresa Filipa Ramôa Gonçalves[1]

1. USF Nova Estação, ACeS Ave/Famalicão, Braga, Portugal.
2. USF Antonina, ACeS Ave/Famalicão, Braga, Portugal.

Citation: Oliveira Peixoto BD, Abreu Gonçalves M, Ferreira da Costa AI, Ramôa Gonçalves TF. Prevalence of vitamin B12 deficiency in patients treated with metformin. Scr Med. 2024 Mar-Apr;55(2):181-6.

Corresponding author:
BRUNO OLIVEIRA PEIXOTO
E: brunopeixxoto@hotmail.com

Abstract

Background/Aim: Metformin has been associated with vitamin B_{12} (cobalamin) deficiency, pushing scientific societies such as the American Diabetes Association and the European Association for the Study of Diabetes to emphasise the need for screening B_{12} levels, without specific metformin doses or exposure durations triggering this screening. Robust data regarding the prevalence of B_{12} deficiency in metformin-treated patients in Portugal are currently lacking. Aim of this study was to identify the prevalence of B_{12} deficiency in a sample of diabetic patients taking metformin. Secondary objectives were determining the minimum dose and minimum and median time exposure time leading to this deficiency and identifying the average duration of metformin use in the patients with this deficiency.
Methods: Descriptive and cross-sectional observational study was performed on a sample of 79 users from a population of 714 diabetic patients on metformin. Inclusion criteria comprised individuals aged 18 or older, receiving metformin for at least 1 month and voluntarily participating in the study. Exclusion criteria included a history of gastrectomy or B_{12} supplementation.
Results: A prevalence of 25.3 % of vitamin B_{12} deficiency was identified in the study sample. Minimum doses of 500 mg of metformin per day and a minimum exposure period of 1 year were associated with B_{12} deficiency. An average exposure time of 5.33 years was identified.
Conclusion: These results align with the prevalence described in the few international studies and should alert physicians to potential clinical manifestations of this deficiency, such as anaemia and neurological symptoms like neuropathy.

Key words: Metformin; Vitamin B_{12}; Diabetes mellitus.

Received: 21 January 2024
Revision received: 25 February 2024
Accepted: 25 February 2024

Introduction

Diabetes mellitus, a chronic metabolic disorder, has reached a prevalence of 537 million in adults aged between 20 and 79 years worldwide in 2021, a number which is expected to increase to 700 million by 2045.[1] Metformin is generally one of the first-line therapy options due to its favourable safety profile, glucose-lowering efficacy and potential cardiovascular benefits.[2] However, a growing body of evidence has raised concerns about its association with vitamin B_{12} (cobalamin) deficiency.

The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) recommend periodic assessment of vitamin B_{12} serum levels in patients on long-term

Copyright © 2024 Peixoto et al. This is an open access article distributed under the Creative Commons Attribution License (CC BY), which permits unrestricted use, distribution and reproduction in any medium, provided the original work is properly cited.

CONTENT

metformin, without specifying exposure times or metformin doses. On the other hand, the Endocrine Society (ES), American Association of Clinical Endocrinology (AACE) and American College of Endocrinology (ACE) advocate for the assessment of vitamin B_{12} levels exclusively in individuals who manifest neuropathic symptoms.[3–5]

The International Society of Nephrology (ISN) recommends the evaluation of serum B_{12} after 4 years of metformin or in those patients with increased risk of deficit (eg, patients with malabsorption syndrome or reduced dietary intake [vegans]). Furthermore, the Canadian Diabetes Association (CDA) advises a periodic measurement of Vitamin B_{12} levels in people taking metformin or with signs or symptoms of deficiency (such as impaired proprioception or peripheral neuropathy).[6]

The prevalence of vitamin B_{12} deficiency in diabetic patients undergoing metformin therapy constitutes a subject of escalating scientific interest and clinical significance due to its association with anaemia and peripheral nerve damage, potentially exacerbating symptoms related to diabetic peripheral neuropathy.[7,8] Understanding the interplay between metformin, diabetes and vitamin B_{12} status is crucial for optimising patient care and mitigating the potential long-term consequences associated with B_{12} deficiency.

The principal aim of this investigation was to evaluate the prevalence of vitamin B_{12} deficiency among diabetic patients taking metformin. The secondary objectives of this study encompassed: appraising the minimal doses of metformin correlated with the occurrence of vitamin B_{12} deficiency and scrutinising the minimal and median durations of exposure to metformin associated with the manifestation of vitamin B_{12} deficiency.

Methods

Participants

The study adhered to the ethical principles outlined in the Declaration of Helsinki and obtained approval from the institutional ethical board at Regional Administration of Health of North of Portugal. All participants provided written informed consent.

In this prospective, on-site investigation, individuals diagnosed with type 2 diabetes, prescribed metformin and presenting for routine consultations with their family physicians during the period from May to August 2023, were invited to participate. The sampling method employed was convenience sampling, selected deliberately to minimise interference with the routine vigilance conducted by family physicians. In instances where patients required blood samples for diabetes monitoring or other purposes, family physicians included B_{12} vitamin analysis in the requisition. The ensuing anonymised results were meticulously entered into a Microsoft Excel® spreadsheet by the family physicians for subsequent analysis by the researchers.

The sample size calculation was executed using the Raosoft® calculator, with a confidence level of 90 %, a margin of error of 10 %, a population size of 714 and a response distribution assumption of 50 %. Consequently, the calculated sample size was determined to be 62 subjects. Ultimately, 79 patients consented to participate in the study.

Inclusion criteria encompassed individuals aged ≥ 18 years, utilising metformin for a minimum of one month and expressing voluntary willingness to partake in the research. Conversely, exclusion criteria encompassed individuals with a history of gastrectomy or those currently supplementing with vitamin B_{12}.

Vitamin B_{12} assessment

Serum levels of vitamin B_{12} were quantified through blood analysis and vitamin B_{12} deficiency was defined as follows: serum B_{12} levels less than 300 pg/mL were considered deficient, levels between 200 and 300 pg/mL were categorised as low-normal and levels equal to or exceeding 300 pg/mL were deemed normal.

There is no universally accepted "gold standard" for the measurement of vitamin B_{12} deficiency, as various methods exist for assessing serum vitamin B_{12} levels, each associated with specific normal values and research findings. A study demonstrating reduced specificity reported that 60 % of patients exhibited symptoms of vitamin B_{12} deficiency with B_{12} levels inferior to 200 pg/mL and 90 % displayed symptoms when the level was below 100 pg/mL.[9] Generally, serum vitamin B_{12} levels can be interpreted as follows: levels greater than 300 pg/mL suggest that B_{12} deficiency is

CONTENT

unlikely (probability of 1 %–5 %); levels between 200 and 300 pg/mL indicate a possible B_{12} deficiency (probability of 5 %–15 %) and levels below 200 pg/mL are consistent with B_{12} deficiency (specificity of 90 %–100 %).[9, 10]

Results

The cohort comprised 79 patients with ages ranging from 38 to 92 years, presenting a mean age of 67 ± 8.26 years. Of the total, 51.9 % (41 patients) were male.

Metformin doses and exposure time

The mean dose of metformin administered was 1642 ± 701 mg/day and the median dose was 2000 mg/day. The dosage range varied from a minimum of 500 mg/day to a maximum of 3000 mg/day. The doses were subsequently classified into four groups, with a predominant proportion of patients (50.6 %, n = 40) receiving metformin doses exceeding 2000 mg per day (Table 1).

Table 1: Metformin doses and exposure time

Metformin	Mean (SD)
Dose (mg/day)	1,642 (701)
< 1000	17.7 (14)
1000 – 1500	16.5 (13)
1500 – 2000	15.2 (12)
≥ 2000	50.6 (40)
Exposure time (years)	7.06 (1.18)
< 5	32.9 (26)
5-10	40.5 (32)
10-15	20.3 (16)
≥ 15	6.3 (4)

The mean duration of metformin use among the participants was 7.06 years ± 1.18 and a median duration of 7 years. The duration ranged from a minimum of 1 year to a maximum of 17 years. The study population was further stratified into four temporal categories: < 5 years: 32.9 % (n = 26); ≥ 5 and < 10 years: 40.5 % (n = 32); ≥ 10 and < 15 years: 20.3 % (n = 16); ≥ 15 years: 6.3 % (n = 4).

Vitamin B_{12} levels

The mean B_{12} levels observed were 412 ± 162 pg/mL, ranging from a minimum of 166 pg/mL to a maximum of 962 pg/mL. Within the study cohort, 25.3 % (n = 20) of individuals exhibited B_{12} deficiency (B_{12} < 300 pg/mL) and this deficiency group was further categorised into distinct subgroups: B_{12} levels ≥ 200 and < 300 pg/mL: 22.8 % and B_{12} < 200 pg/mL: 2.5 %. In addition, the majority of patients (74.7 %) did not exhibit B_{12} deficiency as anticipated. A sub-analysis was performed, comparing the B_{12} deficiency group with the non-deficiency group.

a) Non-deficiency group

The group with normal B_{12} levels was composed of 59 patients, representing 74.7 % of the total population. The mean age in this group was 67.12 ± 8.3 years, mirroring the B_{12} deficiency group. The sex distribution was also similar, with females constituting 52.5 %. The mean B_{12} level in this group was 466.61 ± 153.46 pg/mL, with a range from 303 to 962 pg/mL. This value denoted a mean difference of 212.06 pg/mL when compared to the deficiency group.

In terms of metformin dosage, the mean dose was 1643 ± 753 mg, closely resembling the deficit group (1655 mg). The majority of patients in this group received doses equal to or greater than 2000 mg (49.2 %), a very similar proportion to the deficiency group (55.0 %). Other patients were similarly distributed cross groups: < 1000 mg (18.6 %), ≥ 1000 mg and < 1500 mg (16.9 %) and ≥ 1500 mg and < 2000 mg (15.3 %). The minimum dose observed was 500 mg.

Table 2: Characteristics of the vitamin B_{12} non-deficiency and deficiency groups

Parameter	Non-deficiency group	Deficiency group
N (%)	59 (74.7)	20 (25.3)
Age (years)	67.1 (8.3)	67.4 (9.5)
Sex		
Female	52.5 (31)	35.0 (7)
Male	47.5 (28)	65.0 (13)
Mean B_{12} levels (pg/mL)	466.6 (153.5)	254.5 (38.8)
Mean daily metformin dose (mg)	25.3 (20)	1655 (604)
< 1000	18.6 (11)	15.0 (3)
1000 – 1500	16.9 (10)	15.0 (3)
1500 – 2000	15.3 (9)	15.0 (3)
≥ 2000	49.2 (29)	55.0 (11)
Mean metformin exposure time (years)	7.6 (4.6)	5.3 (3.5)*
Metformin exposure time groups (years)		
< 5	28.8 (17)	40.0 (8)
5-10	37.3 (22)	55.0 (11)
≥ 15	33.9 (20)	5.0 (1)

*The results are presented as mean (standard deviation); * T-test, p = 0.041;*

CONTENT

Regarding the duration of metformin use, the mean time was 7.65 ± 4.56 years. The predominant duration in this group was between ≥ 5 years and < 10 years, accounting for 37.3 %, followed by the segment < 5 years (28.8 %) and >10 years (33.9 %).

b) Deficiency group

The deficiency group comprised 20 patients with a mean age of 67.4 ± 9.5 years. Within this group, males constituted 65 % of the population. The mean B_{12} levels were 254.55 ± 8.8 pg/mL, ranging from a minimum of 166 to a maximum of 297 pg/mL. The mean metformin dosage in this group was 1655 ± 604 mg/day. Among them, the majority (55 %, n = 11) were prescribed doses exceeding 2000 mg/day, with an even distribution (15 %) among the groups receiving less than 1000 mg, between 1000 and 1499 mg and between 1500 and 1999 mg. The minimum prescribed dose was 500 mg/day.

The mean duration of metformin use for the B12 deficiency group was 5.33 ± 3.45 years, demonstrating statistical significance compared to the non-deficiency group (t-test, p = 0.041). The temporal distribution within this group was as follows: 40 % were within the < 5 years category, 55 % in the ≥ 5 to < 10 years category and only 5 % exceeded 10 years. The duration range in the deficiency group spanned from a minimum of 1 year to a maximum of 13 years.

Discussion

In presented study, a prevalence of vitamin B_{12} deficiency of 25.3 % among patients with type 2 diabetes receiving metformin therapy was identified. This high prevalence underscores the imperative need to promptly address this deficiency to alleviate potential symptoms and mitigate overall health repercussions. The observed prevalence aligns with findings from other studies, which report a range of B_{12} deficiency between 6 % and 30 %.

Kim et al identified a prevalence of 22.2 % in a study involving 1111 patients, while Aroda et al, in a prospective study with 1073 participants, reported a prevalence of 19.1 % after 5 years and 20.3 % after 13 years of metformin usage.[10, 11] Additionally, the National Health and Nutrition Examination Survey demonstrated that 41 % of B_{12} deficiency cases among individuals with diabetes were attributable to metformin use.[12] In a Korean study, the prevalence of vitamin B_{12} deficit was lower (9.5 %), emphasising the influence of population differences as a potential bias.

Regarding the duration of metformin use, some studies suggest a cutoff of 4 years for detecting B_{12} deficiency.[13] In presented study, patients with B_{12} deficiency were identified after just 1 year of metformin use. The mean duration under metformin for the B_{12} deficiency group was 5.33 years, consistent with previous data.

The dosage of metformin is also a significant consideration in various studies. For instance, Kim et al reported a decrease in vitamin B_{12} levels by 0.142 pg/mL with a 1 mg increase in metformin, while Beulens et al found a decrease of 0.042 pg/mL.[10, 14] In presented study, doses as low as 500 mg per day were associated with B_{12} deficiency and the majority of the deficiency group (55 %, n = 11) had prescribed doses exceeding 2000 mg/day, aligning with prior data.

In future studies, aim is to replicate these findings on a multicentre or national level to enhance the robustness of presented conclusions. Additional secondary outcomes, including folic acid levels, homocysteine levels, and methylmalonyl-CoA mutase, can also be explored to deepen understanding of B_{12} deficiency.

B_{12} deficiency presents with varied symptoms that may mislead doctors and patients, as neurologic symptoms (characterised by decreased position and vibratory sensation in the extremities accompanied by mild to moderate weakness and hyporeflexia, that may develop in a stocking-glove distribution). It can mimic the diabetic foot symptoms, leading to unnecessary therapy and investigation. Other symptoms such as irritability, depression, weight loss and poorly localised abdominal pain may occur, leading to poor quality of life.[15]

Correcting this disorder is simple, as various B_{12} supplement formulations are available and haematologic abnormalities are usually corrected within 6 weeks. However, doctors should be aware that neurologic symptoms may take much longer and may even become irreversible if they persist for months or years.[15]

CONTENT

Conclusion

The significance of presented results, revealing a 25.3 % prevalence of B_{12} deficiency in patients under metformin, emphasises the importance of physician awareness and proactive management of this side effect to minimise possible symptoms of the patients that may diminish their quality of life.

Ethics

The study was approved by the Ethic Committee of the *Administração Regional de Saúde do Norte* (Northern Regional Health Administration), decision No CE/2024/1, dated 4 January 2024.

Acknowledgement

None.

Conflicts of interest

The authors declare that there is no conflict of interest.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Data access

The data that support the findings of this study are available from the corresponding author upon reasonable individual request.

Author ORCID numbers

Bruno Daniel Oliveira Peixoto (BDOP):
0000-0003-4694-1044
Mariana Abreu Gonçalves (MAG):
0000-0002-3236-367X
Ana Isabel Ferreira da Costa (AIFdC):
0000-0001-7234-2876
Teresa Filipa Ramôa Gonçalves (TFRG):
0009-0008-6848-1556

Author contributions

Conceptualisation: BDOP, MAG, AIFdC, TFRG
Methodology: BDOP, MAG, AIFdC, TFRG
Validation: BDOP, MAG
Formal analysis: BDOP, MAG, AIFdC, TFRG
Investigation: BDOP, MAG
Data curation: BDOP, MAG
Writing - original draft: BDOP, MAG
Writing - review and editing: BDOP, MAG, AIFdC, TFRG
Visualisation: BDOP, MAG
Supervision: BDOP, MAG, AIFdC, TFRG
Project administration: BDOP, MAG

References

1. Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9th edition. Diabetes Res Clin Pract 2019;157:107843. doi: 10.1016/j.diabres.2019.107843.
2. Drzewoski J, Hanefeld M. The current and potential therapeutic use of metformin-the good old drug. Pharmaceuticals (Basel). 2021 Feb 5;14(2):122. doi: 10.3390/ph14020122.
3. American Diabetes Association. Standards of medical care in diabetes-2020 abridged for primary care providers. Clin Diabetes. 2020 Jan;38(1):10-38. doi: 10.2337/cd20-as01.
4. Davies MJ, D'Alessio DA, Fradkin J, Kernan WN, Mathieu C, Mingrone G, et al. Management of hyperglycemia in type 2 diabetes, 2018. a consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2018 Dec;41(12):2669-701. doi: 10.2337/dci18-0033.

CONTENT

5. LeRoith D, Biessels GJ, Braithwaite SS, Casanueva FF, Draznin B, Halter JB, et al. Treatment of diabetes in older adults: an endocrine society* Clinical Practice Guideline. J Clin Endocrinol Metab. 2019 May 1;104(5):1520-74. doi: 10.1210/jc.2019-00198.
6. Diabetes Canada Clinical Practice Guidelines Expert Committee; Lipscombe L, Booth G, Butalia S, Dasgupta K, Eurich DT, Goldenberg R, et al. Pharmacologic glycemic management of type 2 diabetes in adults. Can J Diabetes. 2018 Apr;42 Suppl 1:S88-S103. doi: 10.1016/j.jcjd.2017.10.034.
7. Yang W, Cai X, Wu H, Ji L. Associations between metformin use and vitamin B12 levels, anemia, and neuropathy in patients with diabetes: a meta-analysis. J Diabetes. 2019 Sep;11(9):729-43. doi: 10.1111/1753-0407.12900.
8. Roy RP, Ghosh K, Ghosh M, Acharyya A, Bhattacharya A, Pal M, et al. Study of Vitamin B12 deficiency and peripheral neuropathy in metformin-treated early Type 2 diabetes mellitus. Indian J Endocrinol Metab. 2016 Sep-Oct;20(5):631-7. doi: 10.4103/2230-8210.190542.
9. Stabler SP, Allen RH, Savage DG, Lindenbaum J. Clinical spectrum and diagnosis of cobalamin deficiency. Blood. 1990 Sep 1;76(5):871-81. PMID: 2393714.
10. Kim J, Ahn CW, Fang S, Lee HS, Park JS. Association between metformin dose and vitamin B12 deficiency in patients with type 2 diabetes. Medicine (Baltimore). 2019 Nov;98(46):e17918. doi: 10.1097/MD.0000000000017918.
11. Aroda VR, Edelstein SL, Goldberg RB, Knowler WC, Marcovina SM, Orchard TJ et al. Diabetes Prevention Program Research Group. Long-term metformin use and vitamin B12 deficiency in the diabetes prevention program outcomes study. J Clin Endocrinol Metab. 2016 Apr;101(4):1754-61. doi: 10.1210/jc.2015-3754.
12. Reinstatler L, Qi YP, Williamson RS, Garn JV, Oakley GP Jr. Association of biochemical B_{12} deficiency with metformin therapy and vitamin B_{12} supplements: the National Health and Nutrition Examination Survey, 1999-2006. Diabetes Care. 2012 Feb;35(2):327-33. doi: 10.2337/dc11-1582.
13. Ko SH, Ko SH, Ahn YB, Song KH, Han KD, Park YM, et al. Association of vitamin B12 deficiency and metformin use in patients with type 2 diabetes. J Korean Med Sci. 2014 Jul;29(7):965-72. doi: 10.3346/jkms.2014.29.7.965.
14. Beulens JW, Hart HE, Kuijs R, Kooijman-Buiting AM, Rutten GE. Influence of duration and dose of metformin on cobalamin deficiency in type 2 diabetes patients using metformin. Acta Diabetol. 2015 Feb;52(1):47-53. doi: 10.1007/s00592-014-0597-8.
15. Larry E. Johnson. Vitamin B12 Deficiency. MSD Manual Professional Version. 2024.[Internet]. [Cited: 24-Feb-2024]. Available at: https://www.msdmanuals.com/professional/nutritional-disorders/vitamin-deficiency,-dependency,-and-toxicity/vitamin-b12-deficiency?query=Vitamin%20B12%20Deficiency.

Saroukhani and Omid. Scr Med. 2024 Mar-Apr;55(2):187-92. DOI:10.5937/scriptamed55-47361

ORIGINAL ARTICLE

The Comparison of Streptokinase, an Old Agent, Versus Reteplase for the Re-Tunnellisation of Blocked Cuffed Haemodialysis Catheter

Abbas Saroukhani,[1] Soheil Omid[2]

Abstract

Background/Aim: Catheter occlusion is the most common complication occurring in patients with end-stage renal disease (ESRD) who undergo haemodialysis. The management typically involves the use of local fibrinolytic agents. However, with the emergence of novel agents, the use of older agents has declined. The purpose of the study was to compare the effectiveness of reteplase versus streptokinase (SK) in resolving haemodialysis catheter occlusion.

Methods: This randomised clinical trial involved 100 patients with catheter occlusion who were equally divided into two groups of 50. One group received treatment with reteplase, while the other group received treatment with SK. The occluded catheter in the first group was instilled with 250,000 units (U) of SK, while the second group received 2 U of reteplase and the catheters were left in place for 2-6 h. Successful flushing of the catheter with a velocity of ≥ 200 rounds per minute was considered successful re-tunnelling. The study also evaluated the frequencies of re-injections and drug-related adverse effects.

Results: The success rate of SK versus reteplase did not differ significantly (p = 0.48). However, the required time to inject the agents to achieve appropriate luminal patency was statistically higher in the reteplase-treated group (p = 0.018). None of the patients experienced major adverse effects such as bleeding or anaphylactic reactions.

Conclusion: According to the findings of this study, both reteplase and SK resulted in significant recovery of luminal patency with no adverse effects. However, the lower frequency of re-injections required with SK to achieve successful rationalisation favoured the use of this agent over reteplase. Further studies are strongly recommended.

Key words: Streptokinase; Reteplase; Catheters; Fibrinolytic agents; Haemodialysis.

1. Surgery Department, Isfahan University of Medical Sciences, Isfahan, Iran.
2. Isfahan University of Medical Sciences, Isfahan, Iran.

Citation:
Saroukhani A, Omid S. The comparison of streptokinase, an old agent, versus reteplase for the re-tunnellisation of blocked cuffed haemodialysis catheter. Scr Med. 2024 Mar-Apr;55(2):187-92.

Corresponding author:
SOHEIL OMID
E: dr.soheil.omid@gmail.com
T: +98 9391 408738

Received: 25 October 2023
Revision received: 21 February 2024
Accepted: 21 February 2024

Introduction

Central venous access devices (CVADs) refer to intravenous catheters placed within the central veins for temporary, semi-permanent, or permanent use, typically for haemodialysis in patients with end-stage renal disease (ESRD).[1] It is challenging for 30 % to 67 % of patients who experience occlusion of their haemodialysis catheters, often due to the development of a fibrin sleeve or plug at the catheter tip. In such cases, fibrinolytic agents are used to dissolve the clot and reopen the catheter.[2]

Despite the availability of various thrombolytic options such as alteplase, reteplase and tenect-

Copyright © 2024 Saroukhani and Omid. This is an open access article distributed under the Creative Commons Attribution License (CC BY), which permits unrestricted use, distribution and reproduction in any medium, provided the original work is properly cited.

CONTENT

eplase for managing different thrombotic events, these agents are expensive and not easily accessible, especially in low- to moderate-income countries.[3] At present, alteplase is the preferred fibrinolytic agent approved for treating occluded central venous catheters.[2] However, research on the use of other thrombolytic agents is ongoing.

Reteplase, a deletion mutant of recombinant tissue plasminogen activator, can directly activate plasminogen without complexing with plasminogen.[4] Numerous studies in the literature have explored the use of 0.4 U reteplase per catheter port for 30–60 min, resulting in successful resolution of catheter dysfunction in approximately 85 % – 91 % of cases, with outcomes similar to those of alteplase.[5]

Streptokinase (SK), the first introduced thrombolytic agent, was isolated from β-haemolytic streptococci. Until 1990, it was used for catheter clearance; however, its related complications, such as anaphylaxis (0.1 %) and allergic reactions (5-15 %), led to its limited use.[6] Over time, significant changes have been made in the molecular structure, chemical properties and drug delivery methods of SK, resulting in increased efficacy and reduced immunogenicity and adverse effects of this thrombolytic agent. Due to its low cost and high availability, SK is favoured in developing countries.[7]

The aim of the study was to investigate the therapeutic outcomes of reteplase versus SK for resolving catheter occlusion.

Methods

The current single-blinded randomised clinical trial was conducted on 100 patients admitted due to haemodialysis catheter occlusion at Alzahra Hospital, the tertiary medical centre affiliated with Isfahan University of Medical Sciences during 2019.

Participants eligible for inclusion were over 18 years old, had ESRD, were undergoing haemodialysis treatment, had catheters implanted for over 30 days before occlusion and experienced their first instance of catheter occlusion. Catheter occlusion was defined as difficulty in infusing or withdrawing fluid from the catheter conduit using a 20 mL syringe, or inability to initiate haemodialysis with adequate flow.[8]

Patients with a previous history of central venous stenosis or thrombosis, any mechanical underlying cause for catheter occlusion, hypersensitive reactions to SK or reteplase, use of SK within the previous six months for any reason, high risk of bleeding (recent major surgery, intracranial or spinal injury, active bleeding, aortic aneurysm) lactating or pregnant were not included in the study.

Patients meeting the study criteria were included through convenience sampling until the desired number of participants was achieved. They were then assigned to two-member blocks and randomly allocated to one of the intervention groups using random allocation tables in Microsoft Excel. The patients were blinded to the medication that was administered.

Intervention and outcomes

The patients were divided into two groups, with 50 patients receiving 250,000 units of SK (*Vana Darou Gostar*, Iran) and 50 patients receiving 2 U of reteplase (*Osve Pharmacy*, Iran). The agents were instilled into the catheter and the lumens were not to be in contact with the agents for 6 h after SK and 2 h after reteplase injections.

The primary outcome of the study was to assess luminal patency and successful blood drawing from the catheter into a 20 mL syringe, as well as the possibility of appropriate haemodialysis at a velocity of ≥ 200 rounds per minute.

The secondary outcome included the frequency of thrombolytic use if the first injection did not lead to successful catheter lumen opening.

Data collection and analysis

Additional data on age, gender, duration of ESRD and the site of the embedded catheter were collected from medical records. The collected data were entered into the Statistical Package for Social Sciences (version 22, *IBM Corporation*, Armonk, NY, USA). Categorical statistics were reported as absolute numbers and percentages, while continuous variables were presented as mean and standard deviation. The Chi-square test or Fisher's exact test were used to compare categorical variables and the independent t-test was utilised to compare continuous variables. A p-value of less than 0.05 was considered to be statistically significant.

CONTENT

Results

In the current study, 100 patients in two equal 50-member groups were evaluated. The study population had the mean age of 60.48 ± 13.66 years (range: 19-89) and predominantly consisted of females (58 %). The most prevalent chronic medical diseases in the studied population were hypertension (70 %), diabetes mellitus (67 %), ischaemic heart disease (32 %) and hyperlipidaemia (23 %). Besides, the leading causes of ESRD included diabetes mellitus (64 %), hypertension (17 %), urinary tract infection (10 %), unknown (5 %), autoimmune disease (2 %) and cancer (2 %).

The studied patients were similar in terms of demographic, medical and clinical characteristics including age (p = 0.58), gender (p = 0.84), comorbidities (p > 0.05), the aetiology of ESRD (p > 0.05), duration of ESRD (p = 0.90) and the site of implemented catheter (p = 0.50) (Table 1).

Table 2 shows the thrombolytic therapy related outcomes. Accordingly, the success rate of SK versus reteplase did not differ (p = 0.48). However, the required times to inject the agents in order to achieve appropriate luminal patency were statistically higher in the reteplase treated group (p = 0.018). None of the patients represented major adverse effects of the medications, bleeding and anaphylactic reaction.

Table 1: Demographic and clinical characteristics of the studied population

Variables	Streptokinase treatment group (n = 50)	Reteplase treatment group (n = 50)	p-value
Demographic characteristics			
Age (year), mean ± SD	59.7 ± 13.4	61.2 ± 13.9	0.580 *
Gender (male), n (%)	22 (44 %)	20 (40 %)	0.840 **
Comorbidities, n (%)			
Hypertension	32 (64)	38 (76)	0.190 **
Diabetes mellitus	38 (78)	29 (58)	0.056 **
Ischaemic heart disease	19 (38)	13 (26)	0.190 **
Hyperlipidaemia	12 (24)	11 (22)	0.810 **
The aetiology of end-stage renal disease			
Diabetes mellitus	34 (68)	30 (60)	0.400 **
Hypertension	10 (20)	7 (14)	0.420 **
Urinary tract infection	4 (8)	6 (12)	0.500 **
Autoimmune disease	0 (0)	2 (4)	0.490 #
Cancer	0 (0)	2 (4)	0.490 #
Unknown	2(4)	3 (6)	> 99 #
Clinical characteristics			
ESRD duration (months), mean ± SD	28.0 ± 33.1	27.2 ± 33.9	0.90 *
Site of catheter, n (%)			
Jugular	43 (86)	44 (88)	0.500 **
Femoral	7 (14)	6 (12)	

**: Independent t-test; **: Chi-square test; #: Fisher's exact test; SD: standard deviation; ESRD: end-stage renal disease;*

Table 2: Streptokinase versus reteplase outcomes in the study population

Variables	Streptokinase treatment group (n = 50)	Reteplase treatment group (n = 50)	p-value
Successful luminal patency, n (%)	46 (92)	43 (86)	0.480**
Frequency of injections, mean ± SD	1.1 ± 0.33	1.34 ± 0.56	0.018*
Adverse effects, n (%)			
Bleeding	0 (0)	0 (0)	-
Anaphylactic reaction	0 (0)	0 (0)	

*Independent t-test; **: Chi-square test; SD: standard deviation;*

CONTENT

Discussion

Thrombosis formation in catheter lumens leading to their dysfunction is a common complication, accounting for 37-62 % of ESRD patients undergoing haemodialysis. Despite the high prevalence of this condition, the management and the choice of antithrombotic agents to dissolve the thrombosis with the least potential adverse effects remain a matter of debate. In presented study, aim was to compare the outcomes of two agents, SK versus reteplase. It was found that, despite both agents achieving a similar success rate in restoring appropriate haemodialysis through the patent lumens and having negligible adverse effects, fewer doses of SK were required to effectively dissolve the thrombosis and restore the function of the central venous catheter compared to reteplase.

In presented study, the use of reteplase to reopen the catheter lumen accounted for an 86 % success rate, similar to previous studies that reported a success rate of 85-91 % with the use of alteplase for occluded catheters. However, the specific protocols of these studies may have varied.[5] Most of the studies in the literature applied a dwell time of 0.4 U of reteplase per catheter port for 30–60 min and reported promising outcomes.[9-11] Additionally, a study conducted by Hilleman and colleagues compared high-dose reteplase (2-3 U) with low-dose reteplase (0.5 U) and concluded that the high dose led to significantly superior outcomes than the low dose intervention (91 % versus 84 %).[12] A systematic review on various thrombolytic agents indicated that reteplase outperformed other agents in dissolving occluded catheters.[13]

SK is the oldest plasminogen activator agent used to restore function to occluded catheters. However, its associated complications, such as severe bleeding events and allergic reactions, have discouraged its routine use in this field.[14] Recently, innovations have been applied to the production process of SK to improve its fibrinolytic characteristics, such as genetic manipulations, chemical modifications and domain fusions through the production of chimeric and conjugated SK proteins. These innovations, along with methods such as liposomal entrapment of SK or encapsulation in polyethylene glycol or chitosan nanoparticles, have resulted in the new generation SK with lower immunogenicity and improved fibrin-specific fibrinolytic properties.[7]

In this study, the dwell-lock technique of thrombolytic use, where the thrombolytic agent was instilled into the lumen and left for some hours or the procedure was repeated after an unsuccessful attempt for the first time, was proposed to minimise the potential adverse effects of using thrombolytic agents.[15] This method was associated with no complications after the injections in presented study. Despite the emergence of more novel agents, recent studies have rarely examined SK in dissolving thrombosis. Tahir et al conducted a study in Pakistan comparing SK with urokinase in standard doses and reported successful outcomes for both approaches; however, SK was relatively superior with negligible complications.[6] Another investigation by Wahaj et al compared high dose (375,000 U) versus low dose (225,000 U) SK to restore the patency of a blocked tunnel cuffed catheter. While both doses led to acceptable outcomes, the higher dose significantly led to superior re-canalisation in the first injection, although the success rate did not differ after the second injection.[15]

Conclusion

Older thrombolytic agents, such as SK and reteplase, have shown promise in unblocking haemodialysis catheters. The use of SK with a dwelling-lock technique led to successful outcomes with no complications and reteplase also showed favourable results. Due to the lower cost and the less frequent requirement for reinjection compared to reteplase, SK is preferred in this study. The conclusion suggests the need for further investigations to increase awareness and understanding of SK.

Ethics

The study protocol, which adhered to the tenets of the Helsinki Declaration, was initially proposed to the Isfahan University of Medical Sciences Ethics Committee and approved under the code number IR.MUI.MED.REC.1398.008, dated 17 April 2019. Patients were provided with written information and a verbal explanation about the study before giving their consent to participate. All participants signed a written consent form before taking part in the study.

CONTENT

Acknowledgement

The authors of this manuscript represent their kindest appreciations for the officials of Surgery Department of Isfahan University of Medical Sciences.

Conflicts of interest

The authors declare that there is no conflict of interest.

Funding

The current study was sponsored by Isfahan University of Medical Sciences on the Grant No 397634.

Data access

The data that support the findings of this study are available from the corresponding author upon reasonable individual request.

Author ORCID numbers

Abbas Saroukhani (AS):
0000-0003-2213-263X
Soheil Omid (SO):
0000-0002-0501-4343

Author contributions

Conceptualisation: AS, SO
Methodology: AS, SO
Software: AS, SO
Validation: AS
Formal analysis: SO
Investigation: SO
Resources: AS, SO
Data curation: AS, SO
Writing - original draft: SO
Writing - review and editing: AS, SO
Visualisation: SO
Supervision: AS
Project administration: AS, SO
Funding acquisition: AS

References

1. Thomas M, Nesbitt C, Ghouri M, Hansrani M. Maintenance of hemodialysis vascular access and prevention of access dysfunction: a review. Ann Vasc Surg. 2017 Aug;43:318-27. doi: 10.1016/j.avsg.2017.02.014.
2. Gunawansa N, Sudusinghe DH, Wijayaratne DR. Hemodialysis catheter-related central venous thrombosis: clinical approach to evaluation and management. Ann Vasc Surg. 2018 Aug;51:298-305. doi: 10.1016/j.avsg.2018.02.033.
3. Selçuk E, Arıkan AA, Bayraktar FA. Outcomes of thrombolytic therapy of tunnelled hemodialysis catheter dysfunction. Vasc Endovascular Surg. 2021 Nov;55(8):811-6. doi: 10.1177/15385744211023292.
4. Huang Y, Yu L, Ren J, Gu B, Longstaff C, Hughes AD, et al. An activated-platelet-sensitive nanocarrier enables targeted delivery of tissue plasminogen activator for effective thrombolytic therapy. J Control Release. 2019 Apr 28;300:1-12. doi: 10.1016/j.jconrel.2019.02.033.
5. Wang Y, Sun X. Reevaluation of lock solutions for Central venous catheters in hemodialysis: a narrative review. Ren Fail. 2022 Dec;44(1):1501-18. doi: 10.1080/0886022X.2022.2118068.
6. Tahir T, Raja KM, Azam MN, Arshad AR, Mir AW. Comparison of streptokinase and urokinase for thrombolysis in blocked tunnel cuffed catheter among the patients of chronic renal failure undergoing hemodialysis. Pak Armed Forces Med J. 2022;72(3):792-5. doi: 10.51253/pafmj.v72i3.4112.
7. Roohvand F. Study break: streptokinase for treatment of thrombotic disorders: the end? Or the end of the beginning? Iran Biomed J. 2018 May 1;22(3):140-1. Epub 2017 Nov 14. PMID: 29132206.
8. Lucas TC, Haniel J, Huebner R. Numerical simulation of blood fluid in hemodialysis catheters and its thrombogenic potential. Acta Sci Health Sci. 2019;41:e45613-e. doi: 10.4025/actascihealthsci.v41i1.45613.
9. Castner D. The efficacy of reteplase in the treatment of thrombosed hemodialysis venous catheters. Nephrol Nurs J. 2001 Aug;28(4):403-4, 407-10. PMID: 12143462.
10. Falk A, Samson W, Uribarri J, Vassalotti JA. Efficacy of reteplase in poorly functioning hemodialysis catheters. Clin Nephrol. 2004 Jan;61(1):47-53. doi: 10.5414/cnp61047.
11. Hyman G, England M, Kibede S, Lee P, Willets G. The efficacy and safety of reteplase for thrombolysis of hemodialysis catheters at a community and academic regional medical center. Nephron Clin Pract. 2004;96(2):c39-42. doi: 10.1159/000076397.
12. Hilleman DE, Dunlay RW, Packard KA. Reteplase for dysfunctional hemodialysis catheter clearance. Phar-

CONTENT

macotherapy. 2003 Feb;23(2):137-41. doi: 10.1592/phco.23.2.137.32086.
13. Hilleman D, Campbell J. Efficacy, safety, and cost of thrombolytic agents for the management of dysfunctional hemodialysis catheters: a systematic review. Pharmacotherapy. 2011 Oct;31(10):1031-40. doi: 10.1592/phco.31.10.1031.
14. da Costa ACC, Vieira NNP, Vasques CI, Ferreira EB, Guerra ENS, Dos Reis PED. Interventions for occluded central venous catheters: a meta-analysis. Pediatrics. 2019 Dec;144(6):e20183789. doi: 10.1542/peds.2018-3789.
15. Wahaj, Butt B, Azam N, Raja KM. To ascertain the efficacy, cost effectiveness of streptokinase as intraluminal thrombolytic for occluded tunneled catheters in dialysis patients of a tertiary care hospital-a single center experience. Pak Armed Forces Med J. 2020;70(1):174-9.

CONTENT

Ninković Baroš et al. Scr Med. 2024 Mar-Apr;55(2):193-8. DOI:10.5937/scriptamed55-45967

ORIGINAL ARTICLE

Initial Clinical Manifestations and Early Diagnosis of Basal Cell Skin Carcinoma

Đuka Ninković Baroš,[1, 2] Darko Lukić,[2] Darko Jović,[2, 3] Andrea Stanojević,[4] Spomenka Čutura Paurević[5]

Abstract

Background/Aim: Basal cell carcinoma (BCC) is the most common cancer of the skin. It is believed that increased UV radiation from the sun accounts for almost 90 % of the risk of BCC. There is a growing trend in the incidence of BCC in a younger population. The aim of study was to analyse the initial clinical symptoms of BCC that may be important for the early detection of this skin tumour.

Method: The study was a prospective, multicentre study performed in the period from March 2017 to February 2022. A total of 69 respondents with BCC were analysed. Respondents applied for a targeted examination to examine a suspicious skin lesion (due to certain symptoms) or were diagnosed with BCC by accident, when examining other skin changes. Respondents were divided into 2 groups. The first, Group I (35 respondents), consisted of respondents with nodular BCC. The second, Group II (34 respondents), consisted of respondents with superficial spreading BCC. Initially, a careful history and data on the characteristics, shape and character of the tumour were taken from all respondents. Data on all (even the smallest) initial symptoms and relevant signs of evolution, as well as subjective problems related to the tumour were noted. All respondents underwent dermoscopy of suspected skin changes.

Results: A significant difference was found between the examined groups in the characteristics of bleeding, crust formation and tendency to injury in lesions, where they occur more often in patients with nodular BCC. Symptoms such as burning and flaking occurred significantly more often in patients with superficial spreading BCC ($p < 0.01$), as well as the diameter of lesions over 5 mm ($p < 0.05$).

Conclusion: Early clinical diagnosis of BCC is possible with a tumour diameter of only a few mm. The predominant initial (highly susceptible) symptoms of nodular BCC were initial bleeding and / or scab formation on the lesions, as well as propensity to injury. The superficial spreading form of BCC was often larger than 5 mm in diameter, with more frequent scaling of the lesion, as well as burning and stinging sensations in the tumour area. Itching was observed to be a very common previous occurrence in the BCC initial focus zone in subjects of both study groups. Dermsocopy is a highly reliable diagnostic method for early detection of BCC.

Key words: Basal cell carcinoma; Skin; Clinical diagnosis; Dermoscopy.

1. Skin and Venereal Disease Clinic, University Clinical Centre of the Republic of Srpska, Banja Luka, the Republic of Srpska, Bosnia and Herzegovina.
2. Faculty of Medicine, University of Banja Luka, Banja Luka, the Republic of Srpska, Bosnia and Herzegovina.
3. Health Centre S-Tetic Banja Luka, Banja Luka, the Republic of Srpska, Bosnia and Herzegovina.
4. Department of Urology, General Hospital Doboj, Doboj, the Republic of Srpska, Bosnia and Herzegovina.
5. Health Centre Teslić, Teslić, the Republic of Srpska, Bosnia and Herzegovina.

Citation:
Ninković Baroš Đ, Lukić D, D, Stanojević A, Čutura Paurević S. Initial clinical manifestations and early diagnosis of basal cell skin carcinoma. Scr Med. 2024 Mar-Apr;55(2):193-8.

Corresponding author:
ĐUKA NINKOVIĆ BAROŠ
E: djukaninkovic@yahoo.com

Received: 14 August 2023
evision received: 16 February 2024
Accepted: 16 February 2024

Introduction

Basal cell carcinoma (BCC) of the skin is the most common skin cancer (with an incidence of about 75 % of all skin cancers). At the same time, it is the most common cancer in the human popula-

Copyright © 2024 Ninković Baroš et al. This is an open access article distributed under the Creative Commons Attribution License (CC BY), which permits unrestricted use, distribution and reproduction in any medium, provided the original work is properly cited.

CONTENT

tion. The most common clinical forms of basal cell carcinoma are superficial spreading and nodular basal cell carcinoma.[1] There is consensus regarding the impact of skin damage from UV sunlight on the increased incidence of BCC. That is a reasonable explanation for why the incidence of BCC is particularly high in those parts of the world where increased UV radiation prevails. There are studies that show that the initial damage to the skin from increased UV radiation, which occurred up to the age of 20, with chronic exposure to UV radiation, is a significant risk factor in the development of BCC. At the same time, if the first skin damage from increased UV radiation occurred before the age of ten, the risk of developing BCC skin is relatively higher. There is an evident trend of increasing incidence of BCC in an ever younger population. In addition, there is a clear increased risk of BCC in people with a positive personal or family history of BCC.[1-9]

Methods

This study was a prospective, multicentre study performed in the period from March 2017 to February 2022. A total of 69 respondents with BCC were analysed. Respondents applied for a targeted examination to examine a suspicious skin lesion (due to certain symptoms) or were diagnosed with BCC by accident, when examining other skin changes. Respondents were divided into 2 groups. The first, Group I (35 respondents), consisted of respondents with nodular BCC. The second, Group II (34 respondents), consisted of respondents with the superficial spreading BCC. Initially, a careful personal and family history, risk factors for malignant skin tumours and data on the characteristics, shape and character of the tumour were taken from all respondents, followed by the data that include the characteristics, forms and character of the tumour. Data on all (even the smallest) initial symptoms and relevant signs of evolution, as well as subjective problems related to the tumour were noted. All respondents underwent dermoscopy of suspected skin changes. The observed parameters were both gender and age of the respondents and the anatomical position of the skin BCC.

Data was analysed on IBM SPSS 18.0 software. Normality of data was analysed by Kolmogorov-Smirnov test. Based on the results of test, appropriate parametric/non-parametric test were used. A level of statistical significance was set at $p < 0.05$.

Results

The study included 69 subjects, 35 with basal cell carcinoma of the nodular type and 34 with superficial spreading BCC. In Group I there were 22 (62.8 %) women and 13 (37.2 %) men, while in Group II there were 14 (41.1 %) women and 20 (58.9 %) men. The age of the respondents was from 41 to 90 years and the largest number was between the ages of 71 and 80. The most frequently affected skin region was on the face in both groups of subjects and nodular BCC was most common on the face and back, as shown in Table 1.

Table 1: General characteristics of the respondents and anatomical localisation of basal cell carcinoma

Variables	All patients	Group I	Group II
Number of respondents, N (%)	69 (100.00)	35 (100.00)	34 (100.00)
Gender, N (%)			
Male	27 (39.10)	13 (37.20)	14 (41.10)
Female	42 (60.90)	22 (62.80)	20 (58.90)
Age (years)			
41-50	4 (11.40)	5 (14.70)	9 (13.10)
51-60	5 (14.30)	5 (14.70)	10 (14.50)
61-70	11 (31.40)	10 (29.40)	21 (30.40)
71-80	13 (37.20)	12 (35.30)	25 (36.20)
81-90	2 (5.70)	2 (5.90)	4 (5.80)
Anatomical region of BCC (N, %)			
Head	8 (11.60)	8 (22.90)	0 (0.00)
Face	30 (43.40)	26 (74.30)	4 (11.80)
Neck	1 (1.45)	1 (2.80)	0 (0.00)
Chest	9 (13.10)	0 (0.00)	9 (26.90)
Back	16 (23.20)	0 (0.00)	16 (47.10)
Abdomen	2 (2.90)	0 (0.00)	2 (5.90)
Upper extremity	1 (1.45)	0 (0.00)	1 (2.90)
Hand	0 (0.00)	0 (0.00)	0 (0.00)
Lower extremity	1 (1.45)	0 (0.00)	1 (2.90)
Foot	1 (1.45)	0 (0.00)	1 (2.90)

N (%) – number (percentage), BCC - basal cell carcinoma; Group I consisted of respondents with nodular BCC; Group II consisted of respondents with the superficial spreading BCC;

Clinical characteristics and associated signs are shown in Table 2. Diameter over 5 mm, rapid tumour growth, tumour bleeding, scrab formation flaking, itching, burning, pain and injury were monitored.

CONTENT

Table 2: Distribution of basal cells carcinomas (BCC) according to clinical characteristics and associated signs

Observed parameters	Group I		Group II		p-value*
	Yes	No	Yes	No	
Diameter > 5 mm	7 (20.0)	28 (80.0)	16 (47.1)	18 (52.9)	0.017
Rapid growth	0 (0.0)	35 (100.0)	0 (0.0)	34 (100.0)	
Bleeding	29 (82.8)	6 (17.2)	8 (23.5)	26 (76.5)	< 0.001
Scrab formation	29 (82.8)	6 (17.2)	8 (23.5)	26 (76.5)	< 0.001
Flaking	5 (14.2)	30 (85.8)	22 (64.7)	12 (35.3)	< 0.001
Itch	25 (71.4)	10 (28.6)	29 (85.3)	5 (14.7)	
Burning sensation	7 (20.0)	28 (80.0)	29 (85.3)	5 (14.7)	< 0.001
Twinge sensation	14 (40.0)	21 (60.0)	20 (58.8)	14 (41.2)	
Pain	2 (5.7)	33 (94.3)	1 (2.9)	33 (97.1)	
Injury	25 (71.4)	10 (28.6)	8 (23.5)	26 (76.5)	< 0.001

*Values are presented as N (%) – number (percentage); * t-test of independent samples; Group I consisted of respondents with nodular BCC; Group II consisted of respondents with the superficial spreading BCC;*

Bleeding and appearance of crusts (Student t test; df = 62, p < 0.01) was higher in patients with nodular BCC. Injuries were more often in patients with nodular BCC (df = 67, p = 0.017). BCC was more often over 5 mm in patients with superficial spreading BCC. Peeling and burning sensations were more often in patients with the superficial spreading BCC (p < 0.01 and p < 0.01, respectively).

Discussion

There are various data on the more frequent incidence of BCC in the female or male population. Namely, there are some reports that BCC is more common in male, but also that BCC is more common in women, too.[1] The distribution of presented respondents by gender showed that BCC was more often diagnosed in females, ie in 42 of them (60 %). In general, BCC is more common in people aged 50-70, but there is a visible trend that younger people are also becoming more affected.[1-9] During analysis, the youngest respondent was 40 years old. The youngest female was also 40 years old.

BCC of the skin is more often diagnosed on the face, head, back and pectoral region. Of course, this is not the rule, as it is known that BCC can occur in any anatomical region. The superficial spreading BCC predominantly occurs on the body and back. At the same time, predilection sites for nodular BCC predominantly represent the face and head.[10] There are available reports presenting that the formation of skin BCC tumour foci is associated with immature hair follicle envelope cells.[11] BCC skin formation in anatomical regions covered with hair supports this thesis. Presented research is in terms of the distribution of BCC by anatomical regions in accordance with similar data from the literature.

On the other hand, there is evidence that the formation of BCC of skin is correlated with defects at the level of the sonic hedgehog gene (SHH gene). This thesis is supported by the fact that BCC (true rarely) can also appear as acral BCC of the skin, on the palms or soles and then on the mucous membranes. This favours the thesis of SHH gene abnormalities, because then BCCs do not correlate with hair follicles.[12]

During this research, no BCC was recorded on the acral regions or mucous membranes. Nodular BCC is initially most often diagnosed in the form of a discrete nodule. It is more often described as "mother-of-pearl", almost shiny and small telangiectasias can be seen on it, which is one of the important characteristics of this tumour. Progression is accompanied by small erosions, bleeding and the formation of irritable scabs. After some time, a central ulceration is formed, which is preceded by vascular dilatation. Also, BCC is observed with discrete or quite clear pigmentation. Unpigmented nodular BCCs of the skin are very rare. Tumour progression can take years.[1, 4]

The superficial spreading BCC is also a common skin tumour. This form of BCC can only be diagnosed as a discrete erythematous spot or a vague scaly change. Over time, it expands marginally, forming a rampant edge. Sometimes minor erosions and discrete transient bleeding occur. This form of BCC can also be found in younger people.[1, 4]

CONTENT

Presented research, which focused on the early specifics and symptoms of BCC, showed several important discrete symptoms leading to the formation of a very obvious focus of BCC. Namely, it has been shown that BCC can initially look so uncharacteristic that it too often causes almost no patient attention. In contrast, in a larger number of respondents, in both study groups, BCC was identified with a trivial pimple or other harmless change in the skin.

It has been noticed that careful skin inspection with a careful anamnesis can be of great importance for timely suspicion and early detection of BCC foci. This research has shown that the tendency to bleed and / or scab formation of the initial tumour focus is one of the first highly suspicious symptoms. It turned out that the majority of Group I respondents (29 or 82.8 %) had "unexplained" bleeding in the zone of "harmless, trivial" changes in the skin, which did not deserve the attention of the respondents. However, it was noticed that many respondents rationalised this symptom and diminished its significance. In fact, respondents often associated this significant symptom (diagnosed in both groups in a total of 37, ie 53 % of cases) with previous injuries (which were understood as the cause). Previous injuries were often described by respondents in almost bizarre circumstances, denying that bleeding from the skin change is the result of a possible disease. At the same time, irritation and injury of formed, analysed skin lesions in Group I (observed in 25 or 71.4 % of them) were significantly more common compared to subjects in Group II. This can be explained by the nodular form of the tumour itself.

On the other hand, symptom such as flaking and burning sensation were significantly more frequently reported from Group II respondents. Group II respondents, who described the BCC lesion as a "harmless red spot" after noticing it, were more likely to report flaking in the area of BCC.

Presented analysis showed that BCC at first glance, macroscopically, may indeed look quite harmless and uncharacteristic, but with a precise examination that includes dermoscopy, the BCC tumour focus can be detected at the earliest stage, when it is only a few mm in diameter. Neglected forms can be much larger and of course do not present a diagnostic challenge. During this analysis in Group I, BCC foci were diagnosed in diameters that were more often up to 5 mm in diameter. On the contrary, in Group II, BCC lesions were more often diagnosed in diameter over 5 mm. The reason for this is probably the anatomical distribution of the superficial spreading BCC, as well as the inconspicuous appearance of this form of BCC in the initial phase.

Both groups (without statistical difference) had a frequent itching sensation in the lesion area. Itching was reported in a total of 54 (78 %) respondents. Attempts to eliminate itching with light scratching resulted in petechiae short-term bleeding. Several respondents from Group II noticed traces of blood on their clothes after lightly scratching the BCC lesion during the night, so that was the motive for coming for the examination.

In all cases of BCC, when tumour is detected and removed in a timely manner, the treatment has a very good prognosis. On the other hand, when BCC skin is not recognised in time and the patient is not adequately treated BCC skin easily becomes a big problem. At the same time, frustration with the treatment of BCC patients is the knowledge that, despite proper treatment in a significant number of patients (30-50 %) BCC of skin may reappear.[1] Due to this nature of the disease, BCC can be described as a low or high risk tumour. This assessment is based on the characteristics of each BCC which include: tumour size and type, anatomical position, tumour borderline condition, growth factor and histopathological character, principle of treatment from previous BCC as well as possible existence of immunosuppression. Otherwise, BCC skin can be very slow and last for years but also it can be locally very aggressive.[1, 13-16]

Presented analysis showed that both analysed types of BCC of the skin can be diagnosed at the earliest stage, provided that early manifestations and symptoms are recognised, which often act extremely discreetly. This means that the treatment undertaken in such an early phase of tumour detection offers the possibility of timely, optimal treatment and allows local removal of the tumour in its entirety without functional, aesthetic and mental comorbidity.

In all cases of discrete skin changes of a macroscopically debatable nature, dermoscopy is available today. It is a non-invasive, *in vivo* microscopy of skin changes, very effective and

CONTENT

welcome for early detection of BCC. Dermoscopy is primarily intended for the analysis and diagnosis of pigmented skin changes and melanoma. Dermoscopy visualises details, in suspicious skin lesions, that are macroscopically inaccessible. Dermoscopic examination is a highly reliable diagnostic method for BCC.[17-26]

This research confirmed the importance and reliability of dermoscopy because it was shown that it was in full correlation with the pathohistological findings of the analysed respondents. Several of respondents applied antibiotics to the initial BCC outbreak on their own initiative, which partially masked the lesions and made the diagnosis more difficult. This is a detail that should be considered in anamnestic interview in patients with suspected BCC lesions.

Conclusion

Early clinical diagnosis of BCC is possible with a tumour diameter of only a few mm. The predominant initial (highly susceptible) symptoms of nodular BCC were initial bleeding and / or scab formation on the lesions, as well as propensity to injury. The superficial spreading form of BCC was often larger than 5 mm in diameter, with more frequent scaling of the lesion, as well as burning and stinging sensations in the tumour area. Itching was observed to be a very common previous occurrence in the BCC initial focus zone in subjects of both study groups. Dermsocopy is a highly reliable diagnostic method for early detection of BCC.

Ethics

The protocol of this study was approved by the Ethics Committee of the University Clinical Centre of the Republic of Srpska, decision No 01-19-57-2/24, dated 14 February 2024.

Acknowledgement

None.

Conflicts of interest

The authors declare that there is no conflict of interest.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Data access

The data that support the findings of this study are available from the corresponding author upon reasonable individual request.

Author ORCID numbers

Đuka Ninković Baroš (ĐNB):
0009-0003-7272-7663
Darko Lukić (DL):
0009-0000-2136-9067
Darko Jović (DJ):
0000-0002-1357-8210
Andrea Stanojević (AS):
0009-0007-9664-1652
Spomenka Čutura Paurević (SČP):
0009-0005-1103-4016

Author contributions

Conceptualisation: ĐNB, AS
Methodology: DL
Software: SČP
Validation: DL
Formal analysis: DL
Investigation: ĐNB, DL, DJ
Resources: ĐNB
Data curation: ĐNB
Writing - original draft: ĐNB
Writing - review and editing: ĐNB

CONTENT

References

1. Bandić J. The reliability of dermoscopic pigmented skin lesions differentiation [dissertation]. Banja Luka: Faculty of Medicine, University of Banja Luka, 2017; p. 12-44.
2. Cameron MC, Lee E, Hibler BP, Barker CA, Mori S, Cordova M, et al. Basal cell carcinoma: Epidemiology, patophisiology, clinical and histological subtypes, and disease associations. J Am Acad Dermatol. 2019;80(2):303-17. doi: 10.1016/j.jaad.2018.03.060.
3. Drucker AM, Adam GP, Rofeberg V, Gazula A, Smith B, Moustafa F, et al. Treatments of primary basal cell carcinoma of the skin: a systematic review and network meta-analysis. Ann Intern Med. 2018 Oct 2;169(7):456-66. doi: 10.7326/M18-0678.
4. Kamath P, Darwin E, Arora H, Nouri KA. Review on imiquimod therapy and discussion on optimal menagement of basal cell carcinomas. Clin Drug Investig. 2018;38(10):833-99. doi: 10.1007/s40261-018-0681-x.
5. Martens MC, Seebode C, Lehmann J, Emmert S. Photocarcinogenesis and skin cancer prevention strategies: an update. Anticancer Res. 2018;38(2):1153-8. doi: 10.21873/anticanres.12334.
6. Clark CM, Furniss M, Mackay-Wiggan JM. Basal cell carcinoma: an evidence-based treatment update. Am J Clin Dermatol. 2014;15(3):197-216. doi: 10.1007/s40257-014-0070-z.
7. Bath-Hextall F, Ozolins M, Armstrong SJ, Colver GB, Perkins W, Miller PS, et al; Surgery versus Imiquimod for Nodular Superficial basal cell carcinoma (SINS) study group. Surgical excision versus imiquimod 5% cream for nodular and superficial basal-cell carcinoma (SINS): a multicentre, non-inferiority, randomised controlled trial. Lancet Oncol. 2014 Jan;15(1):96-105. doi: 10.1016/S1470-2045(13)70530-8.
8. van Loo E, Mosterd K, Krekels GA, Roozeboom MH, Ostertag JU, Dirksen CD, et al. Surgical excision versus Mohs' micrographic surgery for basal cell carcinoma of the face: A randomised clinical trial with 10 year follow-up. Eur J Cancer. 2014 Nov;50(17):3011-20. doi: 10.1016/j.ejca.2014.08.018.
9. OchoM, Lee J, James CL, Marshman G. Huilgol SC. Scalp basal cell carcinoma: review of 2,202 cases. Dermatol Surg. 2016;42:834-41. doi: 10.1097/DSS.0000000000000783.
10. Kossard S, Epstein EH, Cerio R, Yu LL, Weedon D. Basal cell carcinoma. In: LeBoit PE, Burg G, Weedon D, Sarasain A. (Eds): World Health Organization Classification of Tumours. Pathology and genetics of skin tumours. Lyon, France: IARC Press, 2006; pp. 13-19.
11. Youssef KK, Van Keymeulen A, Lapouge G, Beck B, Michaux C, Achouri Y, et al. Identification of the cell lineage at the origin of basal cell carcinoma. Nat Cell Biol. 2010;12:299-305. doi: 10.1038/ncb2031.
12. Crowson AN. Basal cell carcinoma: biology, morphology and clinical implications. Mod Pathol. 2006 Feb;19 Suppl 2:S127-47. doi: 10.1038/modpathol.3800512.
13. Dandurand M, Petit T, Martel P, Guillot B; ANAES. Management of basal cell carcinoma in adults Clinical practice guidelines. Eur J Dermatol. 2006 Jul Aug;16(4):394-401. PMID: 16935797.
14. Khan L, Breen D, Zhang L, Balogh J, Czarnota G, Lee J, et al. Predictors of recurrence after radiotherapy for non-melanoma skin cancer. Curr Oncol. 2014 Apr;21(2):e326-9. doi: 10.3747/co.21.1727.
15. Kadouch DJ, van Haersma de With A, Limpens J, van der Wal AC, Wolkerstorfer A, et al. Is a punch biopsy reliable in subtyping basal cell carcinoma? A systematic review. Br J Dermatol. 2016 Aug;175(2):401-3. doi: 10.1111/bjd.14458.
16. Luz FB, Ferron C, Cardoso GP. Surgical treatment of basal cell carcinoma: an algoritam based on the literature. An Bras Dermat. 2015;90(3):377-83. doi: 10.1590/abd1806-4841.20153304.
17. Wozniak-Rito A, Zalaudek I, Rudnicka L. Dermoscopy of basal cell carcinoma. Clin Exp Dermatol. 2018;43:241-7. doi: 10.1111/ced.13387.
18. Sgouros D, Apalla Z, Ioannides D, Katoulis A, Rigopoulos D, Sotiriou E, et al. Dermoscopy of common inflammatory disorders. Dermatol Clin. 2018;36(4):359-68. doi: 10.1016/j.det.2018.05.003.
19. Merkel EA, Amin SM, Lee CY, Rademaker AW, Yazdan P, Martini MC, et al. The utility of dermoscopy-guided histologic sectioning for the diagnosis of melanocystic lesions. A case control study. J Am Acad Dermatol. 2016;74(6):1107-13. doi: 10.1016/j.jaad.2016.01.002.
20. Choo JY, Bae JM, Lee JH, Lee JY, Park YM. Blue-gray blotch: A helpful dermoscopic finding in optimal biopsy site selection for true vasculitis. J Am Acad Dermatol. 2016;75(4):836-8. doi: 10.1016/j.jaad.2016.05.022.
21. Lallas A, Argenziano G, Kyrgidis A, Apalla Z, Moscarella E, Longo C, et al. Dermoscopy uncovers clinically undetectable pigmentation in basal cell carcinoma. Br J Dermatol. 2014 Jan;170(1):192-5.
22. Lallas A, Moscarella E, Argenziano G, Longo C, Apalla Z, Ferrara G, et al. Dermoscopy of uncommon skin tumours. Australas J Dermatol. 2014 Feb;55(1):53-62. doi: 10.1111/ajd.12074.
23. Fargnoli MC, Kostaki D, Piccioni A, Micantonio T, Peris K. Dermoscopy in the diagnosis and management of non-melanoma skin cancers. Eur J Dermatol. 2012 Jul-Aug;22(4):456-63. doi: 10.1684/ejd.2012.1727.
24. Sanchez-Martin J, Vazquez-Lopez F, Perez-Oliva N, Argenziano G. Dermoscopy of small basal cell carcinoma: study of 100 lesions 5 mm or less in diameter. Dermatol Surg. 2012 Jun;38(6):947-50. doi: 10.1111/j.1524-4725.2012.02358.x.
25. Kim DP, Kus KJB, Ruiz E. Basal cell carcinoma review. Hematol Oncol Clin North Am. 2019 Feb;33(1):13-24. doi: 10.1016/j.hoc.2018.09.004.
26. Reiter O, Mimouni I, Gdalevich M, Marghoob AA, Levi A, Hodak E, et al. The diagnostic accuracy of dermoscopy for basal cell carcinoma: A sysematic review and meta-analysis. J Am Acad Dermatol. 2019;80(5):1380-8. doi: 10.1016/j.jaad.2018.12.026.

CONTENT

Tiwana et al. Scr Med. 2024 Mar-Apr;55(2):199-217. DOI:10.5937/scriptamed55-48730

REVIEW ARTICLE

The Involvement of Reactive Oxygen Species in Causing Chronic Cardiovascular and Neurodegenerative Diseases and Some Cancers

Jasneet K Tiwana,[1] Anureet K Shah,[2] Naranjan S Dhalla[1]

Abstract

An increase in the occurrence of different infectious and chronic diseases as well as aging population has resulted in poor human health and decline in the quality of life all over the world. In fact, chronic diseases, which are partially resistant to currently available drugs are long lasting health hazards and require ongoing medical attention. Major causes of increase in these diseases are considered to be changes in the environment as well as diets and lifestyle. Particularly, there has been changes from a simple, nutritious, low- calorie diet and active lifestyle to a complex and processed food rich in high calories accompanied by a sedentary lifestyle and unhealthy living habits. Since high-calorie diets and inactive lifestyle are known to promote the production of reactive oxygen species (ROS) in the body, it is likely that oxidative stress and associated inflammation may be intimately involved in enhancing the resistance of several disorders to the existing therapeutic interventions and thus promoting the occurrence of chronic diseases. A thorough review of literature regarding the pathogenesis of some major chronic diseases including cardiovascular disease like heart failure, neurodegenerative disorder like Alzheimer's disease and various types of cancer has revealed that these health hazards are associated with increased oxidative stress, production of pro-inflammatory chemicals such as nitric oxide and some cytokines, as well as formation of some toxic substances such as advanced glycation end products. It is thus evident that extensive research work by employing genetic, immunological and nutraceutical approaches, needs to be carried out for developing some novel antioxidants with anti-inflammatory activities for reducing the incidence of chronic diseases. In the meantime, it would be prudent for patients with chronic diseases to pursue the preventive measures involving reduced intake of high calorie diet and following an active lifestyle.

Key words: Heart failure; Cancer; Alzheimer's disease; Oxidative stress; Inflammation; Low calorie diet; Active lifestyle.

1. Institute of Cardiovascular Sciences, St. Boniface Hospital Albrechtsen Research Centre, Department of Physiology and Pathophysiology, Max Rady College of Medicine, University of Manitoba, Winnipeg, Canada.
2. Department of Nutrition and Food Science, California State University, Los Angeles, USA.

Citation:
Tiwana JK, Shah AK, Dhalla NS. The involvement of reactive oxygen species in causing chronic cardiovascular and neurodegenerative diseases and some cancers. Scr Med. 2024 Mar-Apr;55(2):199-217.

Corresponding author:
NARANJAN S DHALLA
E: nsdhalla@sbrc.ca

Received: 15 January 2024
Revision received: 24 February 2024
Accepted: 24 February 2024

Introduction

Chronic disease conditions are health hazards, which are long-lasting and persistent in their effects on diverse body functions. Such a terminology for chronic diseases has a large degree of variations in use within the professional community because the Center for Disease Control classifies heart disease, stroke, cancer, diabetes and obesity as chronic diseases, whereas Centers

Copyright © 2024 Tiwana et al. This is an open access article distributed under the Creative Commons Attribution License (CC BY), which permits unrestricted use, distribution and reproduction in any medium, provided the original work is properly cited.

CONTENT

for Medicare and Medicaid Services have a more extensive list of chronic diseases including neurodegenerative diseases. These differences have created a great deal of confusion in estimating the impact of chronic diseases, the cost of these disorders and interventional measures for reducing these health hazards.[1] It needs to be emphasised that chronic disease conditions are different from acute disease conditions as these affect multiple organs of the body and are not be fully responsive to various medications and treatments.[2] Chronic diseases require ongoing medical attention and limit daily life activities like social interaction, personal movements, eating or sleeping.[3] Some of the major examples of chronic diseases include arthritis, diabetes, hypertension, autoimmune diseases and acquired immunodeficiency syndrome, in addition to cardiac diseases, cancer and neurodegenerative disorders.

Chronic diseases are the leading cause of mortality worldwide and their occurrence is not confined to any particular social or religious class as well as any geographical region.[4] In fact, chronic diseases are generally considered to be the consequence of poor nutrition with modern foods. It may be noted that modern foods are high in calories, fats and salt but low in fibres[5] as compared to traditional foods, which are rich in micronutrients, macronutrients, carotenoids, fibres, vitamins and minerals.[6] The methods of preparing, processing and preserving modern foods are also considered to produce more toxic ingredients such as advanced glycation end products (AGEs) and reactive oxygen species (ROS) in comparison to the traditional procedures.[7,8] Other reasons include a sedentary lifestyle, excessive use of alcohol and tobacco, socioeconomic stress, genetics, race, ethnicity and religious habits.[9,10] The aging population suffering from multiple chronic conditions is adding to the existing burden on healthcare services all over the world.[11]

In view of the poor quality of life of patients with chronic diseases, it is crucial that special attention be paid to formulate some appropriate strategies to deal with this devastating health problem. Particularly, it is noteworthy that the rate of chronic diseases is becoming high due to aging population and most of these patients are more resistant to the existing pharmacotherapy. Thus, there is an urgent need not only to understand the pathogenesis of diverse chronic diseases but also to develop novel drugs for their treatment in aging population. It will also be prudent to consider some alternative procedures and interventions such as nutritional and lifestyle modifying approaches for the purpose of preventive medicine. The present article is, therefore, intended to review the existing information regarding some of the chronic diseases namely, cardiovascular and neurodegenerative diseases as well as some types of cancer, which are major causes of mortality. Although the pathogenesis and modification factors for the development of chronic diseases are different from each other, the role of a few pathogenic mechanisms will be described to evaluate if there is any commonality for the occurrence of these health hazards. Some discussion will also centre around the effectiveness of newer pharmacotherapy for the treatment of each disease in addition to assessing the beneficial effects of some nutritional and lifestyle approaches.

Role of oxidative stress and inflammation in chronic diseases

a. Sources of ROS production

The production of ROS occurs due to leaking electrons from the mitochondrial electron transport chain during the metabolic process of energy production. The free oxyradicals thus formed react with other mitochondrial proteins to produce more ROS such as superoxide radicals, hydroxyl radicals and hydrogen peroxide.[6] ROS are also generated by the activation of NADPH oxidases,[12] which play important roles in many degenerative diseases. The excessive production of ROS leads to oxidative stress in the body.[13-15] The sources of ROS can be exogenous such as UV radiation; pollutants including paraquats, quinones, phenols; carcinogens and many chemotherapeutic drugs. In addition, ROS can also be produced endogenously in the body by intracellular enzymes like flavoenzyme ER01 in the endoplasmic reticulum, cytochrome p450 enzyme, lipoxygenases and nitric oxide (NO) synthase. These molecular targets are considered suitable for the development of interventions for disease prevention.[16] The activation of NO synthase leads to excessive production of NO, which reacts with superoxide radicals to form peroxynitrite for inducing nitrosative stress.[15] This pathogenic factor damages cells by oxidising free thiols and nitrating tyrosine residues leading to cardiovascular disease.[17] The

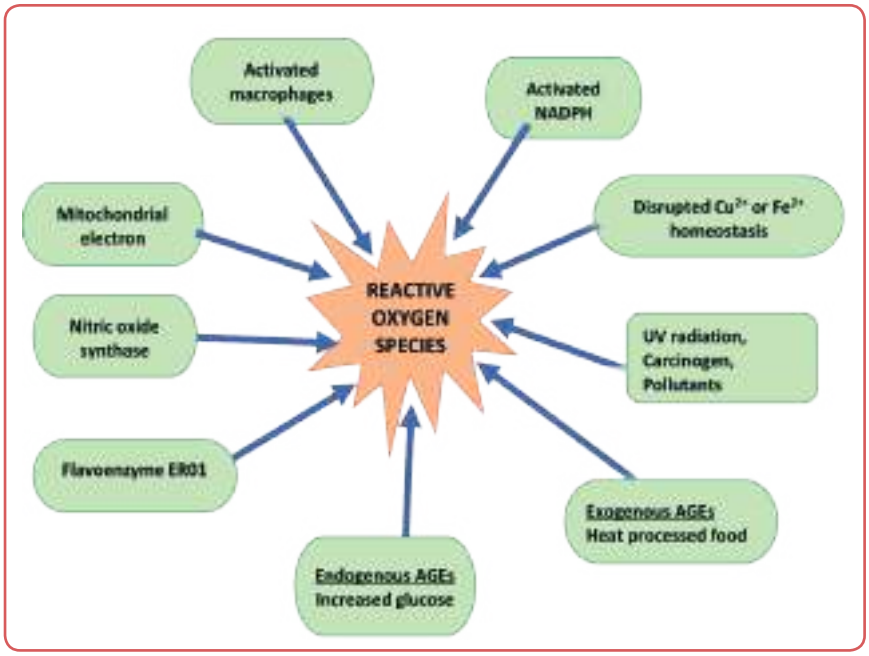


Figure 1: Various sources for the generation of reactive oxygen species
UV – ultraviolet; AGEs – advanced glycation end products;

intracellular production of ROS in mitochondria occurs through enzymes like dihydroorotate dehydrogenase, glycerophosphate dehydrogenase, NADPH oxidase, monoamine oxidase, xanthine oxidase as well as Complex 1 and 3 of the electron transport chain.[18] There is also existing evidence that mitochondria have evolved as an antioxidant system which prevents these organelles from oxidative damage due to both internal and external ROS with the help of enzymes like superoxide dismutase and glutathione peroxidase.[15, 19] The mitochondrial antioxidant system allows only a small part of the endogenously produced ROS in mitochondria to escape from there to limit the production of oxidative stress in the cell.[19] The production of ROS from various sources is shown in Figure 1.

Moderate levels of ROS and NO have been observed to activate the intracellular signalling reactions for beneficial effects.[13-15] ROS are involved in ovulation[20] and T cell-mediated immunity in the body[21] whereas NO has been demonstrated to regulate cardiovascular and neuronal functions in addition to involvement in apoptosis and cell necrosis.[22] ROS have also been shown to oxidise cholesterol, proteins, carbohydrates and vitamins leading to the production of toxic and mutagenic compounds such as AGEs which are responsible for many diseases.[15, 23, 24] AGEs also undergo oxidation and dehydration to cause an increase in oxidative stress for the induction of chronic diseases.[22] AGEs are exogenously formed in heat-processed foods[25] as well as endogenously formed by high amounts of sugars in the body, mostly fructose.[26] The carbohydrates-rich foods, as well as fish, legumes, vegetables, fruits and whole grains have been observed to contain lower levels of AGEs as compared to processed foods with high fat that lead to increased plasma ceramide levels.[26] The preparation of food at high temperatures for a longer period of time also leads to the production of a higher amount of AGEs as compared to other methods such as steaming and boiling.[25] It is pointed out that breakdown of homeostasis for metal ions, which are a part of many active sites in proteins has been reported to cause the production of uncontrolled amounts of AGEs in the body.[27]

b. Role of inflammation

It is now well known that chronic diseases are also caused by inflammation, which is an immune response of the body against foreign pathogens by the host cells. One of the main causes of inflammation is the activation of macrophages and cells like polymorphonuclear neutrophils (PMNs) that are involved in the cellular defences of the host. These also lead to the production of pro-inflammatory mediators for further increasing inflammation and oxidative stress by the formation of more ROS and reactive nitrogen species (RNS).[13] ROS are produced to clear the body of pathogens by causing an increase in inflammation but may also cause tissue injury to the host cell and an increase in the production of RNS to result in DNA damage and formation

CONTENT

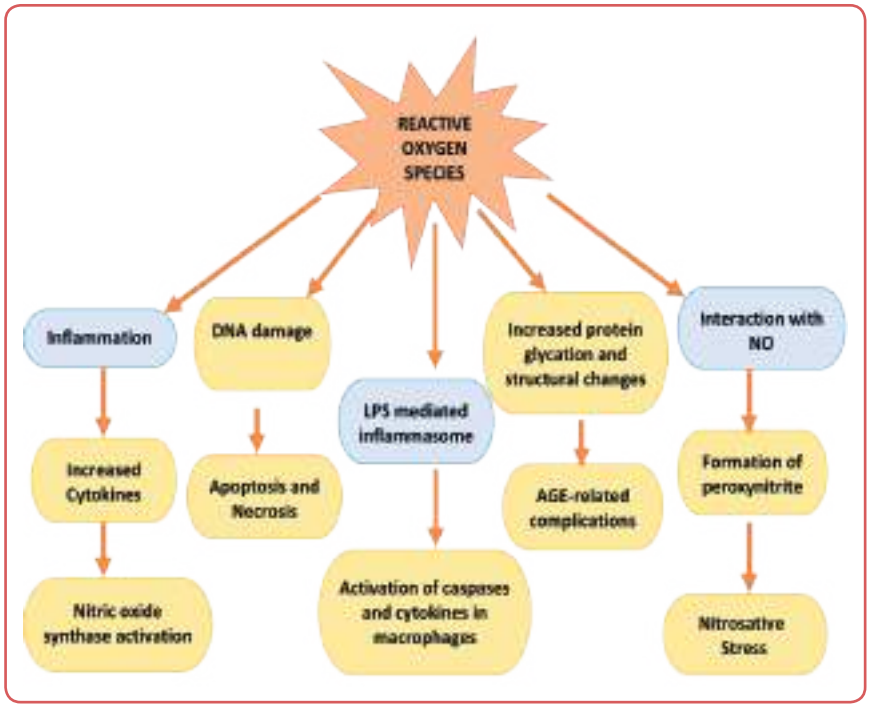


Figure 2: Some effects of reactive oxygen species
LPS- lipopolysaccharide; NO – nitric oxide; AGEs – advanced glycation end products; DNA – deoxyribonucleic acid;

of AGEs causing dysfunction in cellular processes and leading to death of cells by apoptosis and necrosis.[28] Inflammatory cytokines cause activation of myeloperoxidase and NO synthase which also increase the nitrosative stress.[15] The dietary AGEs have been observed to be related to the levels of C-reactive protein and serum AGEs and these have been suggested to be responsible for inflammatory reactions during the development of several chronic diseases.[29] Some of the adverse effects of excessive amount of ROS are shown in Figure 2.

Excessive levels of NO have been shown to result in septic shock and cytotoxicity induced by activated macrophages in different chronic diseases.[30-32] Activated macrophages in the inflamed area are also known to produce ROS and tissue damage due to elevated levels of oxidative stress.[33] Increased oxidative stress and inflammation have also been shown to be related to various human diseases like diabetes mellitus, neurodegenerative diseases, cancer, rheumatoid arthritis, cataracts, cardiovascular diseases, respiratory diseases and aging.[34] Mitochondrial-derived ROS have been reported to be involved in the production of proinflammatory cytokines as well as in the regulation of inflammasome which activates inflammatory caspases in macrophages.[33] Different diseases also result from disrupted homeostasis of metals such as copper and iron which promote the formation of RNS and ROS. These metals are also responsible for lipid peroxidation leading to the development of cancer and neurodegenerative diseases.[35] The regulation of glutathione both in reduced (GSH) and oxidised (GSSG) forms, is one of the most important antioxidant systems which, when compromised in the presence of excess ROS and RNS, result in an increase in disease conditions and symptoms.[12, 36] Mitochondrial dysfunction has been shown to occur upon the generation of high levels of both oxidative stress and inflammation leading to mitosis and mitophagy.[18] Although it is difficult to indicate the cause-effect relationship between the development of oxidative stress and inflammation, it is evident that both these pathogenic processes are intimately involved in the genesis of several chronic diseases.

Role of oxidative stress in cardiovascular diseases

Cardiovascular diseases include many health disorders and syndromes such as angina, myocardial infarction, stroke, heart failure, arrhythmias, congenital heart disease, myocarditis and valvular heart disease.[36, 37] Various factors are considered as the reasons for the onset of cardiovascular diseases, some of these include smoking, diabetes, high blood pressure, sedentary lifestyle, obesity, high- calorie foods, poor nutrition and high cholesterol levels.[36-39] Collectively, car-

diovascular ailments are the number one cause of global deaths as an estimated 17.9 million deaths occurred in 2019.[39] Cardiovascular diseases are also the second leading cause of death in Canada.[40] Globally, 32 % of mortality is accounted for by cardiovascular diseases and the rate of spread is expected to increase due to high risk factors in low-income countries.[39-41] It is noteworthy that some studies have shown that an increase in oxidative stress is a causative factor for programmed and unprogrammed cell death of cardiomyocytes as well as molecular and cellular changes in the heart. Oxidative stress has also been associated with abnormalities related to calcium handling in cardiomyocytes and the loss of sensitivity of myofilaments to calcium. Nitrosative stress due to activation of NO synthase is one of the major causes of endothelial dysfunction seen in cardiac diseases. Palmitoyl carnitine oxidation which occurs due to increased fatty acid uptake by the myocardial tissue also results in increased ROS production and structural changes in mitochondria of cardiac cells.[15] Thus, it appears that high mortality due to cardiovascular disease may be related to increased levels of both oxidative and nitrosative stress in the body.

a. Production of oxidative stress in the heart

Mineralocorticoid receptors (MR) are corticosteroid receptors, the overactivation of which has been observed in many cardiovascular diseases.[42-45] The activation of these receptors occurs through the stimulation of Rac1 GTPase by increased oxidative stress in a ligand-independent manner. The activation of Rac1 induces an increase in the transcription of MR and development of cardiac dysfunction. Furthermore, the activation of Rac1 leads to increased translocation of MR causing accumulation of MR inside the nucleus.[42, 46] The activated MR then recruit NADPH oxidase (NOX), which increases the production of ROS to cause cardiac dysfunction.[46, 47] This process also produces DNA damage in the pressure-overloaded heart and is considered to be one of the major sources of increased oxidative stress in the failing heart.[15, 47] Increased production of ROS through the activation of Rac1 in cardiomyocytes forms a feed-forward loop, causing cardiomyocyte damage.[43] In addition, oxidative stress alters nuclear MR translocation through which MR signal transduction is activated to increase oxidative stress.[41, 42, 48] It should be noted that the family of NOX enzymes, which are transmembrane proteins, play very important roles in the development of oxidative stress. Acute myocardial infarction and reperfusion injury are associated with activation of phagocytic NO synthase which also results in an increase in ROS.[15] The ROS thus formed act on various targets like protein tyrosine kinases, protein kinase C, protein tyrosine phosphatases, calcium channels as well as MAP kinases and transcription factors to produce a wide variety of cardiovascular abnormalities.[17] These ROS specific redox signals have been shown to cause cell death and apoptosis in cardiovascular diseases.[49]

Angiotensin II, catecholamines and the pro-inflammatory cytokine, TNF-a, have been reported to produce abnormal stimulation of nonphagocytic NO synthase, which can lead to collagen deposition, fibrosis and heart failure.[15] The activation of guanine protein- coupled angiotensin receptors (AT_1R) by angiotensin II also leads to the transactivation of endothelium growth factor (EGF) receptors through ROS.[49] When angiotensin II binds the AT_1R, it causes the receptor to get into the lipid raft and results in the formation of ROS from a complex involving Rac1. The increased ROS then promote phosphorylation of tyrosine residues of the EGF receptor in a calcium-dependent manner.[50] This phosphorylated EGF receptor acts as a scaffold for other signal molecules and forms a signalling platform, which activates extracellular signal-regulated kinase 1/2 (ERK1/2) as well as Akt, and leads to vascular hypertrophy.[17, 49, 51] Such a change results in the assembly of downstream signalling complexes, which also leads to vascular hypertrophy and hypertension.[49, 52, 53] Angiotensin II generates ROS by activating various signalling pathways associated with phospholipase C, phospholipase D and phospholipase A2. Activation of phospholipase A2 releases arachidonic acid which results in the production of ROS. When phospholipase C is activated, it leads to the hydrolysis of phosphatidylinositol 4,5-bisphosphate to inositol 1,4,5-triphosphate (IP3) and diacylglycerol (DAG).[54] The formation of IP3 triggers the IP3-Ca^{2+} release pathway whereas DAG activates protein kinase C (PKC), both of which produce an increase in ROS by activating the NADPH oxidase complexes.[50] Oxidative stress has been demonstrated to cause more angiotensin II to bind to AT_1R and more intense intracellular accumulation of IP3 due to higher levels of activation of the phospholipase C pathway. Oxidative stress also increases AT_1R and sodium-hydrogen exchanger 3 in proximal tubular cells. Thus, oxidative stress makes phospholipase C more sensitive to angiotensin II ef-

CONTENT

fects and increases sodium retention in the body to elevate the blood pressure. Because there is an increase in the expression of AT_1R by angiotensin II, it has been suggested that the presence of a positive feedback loop for this hormone may also increase the blood pressure further.[55]

Angiotensin II has been observed to cause deletion in mitochondrial DNA and induce cardiomyocyte autophagy. High levels of circulating angiotensin II for a long time produce calcium overload in mitochondria, decrease mitochondrial function and increase oxidative stress.[15] It may be noted that monoamine oxidase in mitochondria is also a major source of ROS production and leads to the degradation of neurotransmitters like norepinephrine, dopamine, epinephrine and serotonin. Some heart diseases are associated with increased plasma levels of serotonin and catecholamines, which may be degraded by monoamine oxidase to increase the production of ROS and worsening the heart disease.[15] The vascular layers of the cell like endothelium and adventitia also produce ROS and thus play an important role in regulating vascular tone and inflammation. These ROS act as mediators and regulators of vascular functions[17, 51, 56] and when present in excess, these can lead to vascular cell damage, necrosis and apoptosis by directly oxidising the structural molecules.[17, 56]

b. Cardiac effects of oxidative stress

Both oxidative and nitrosative stress have been reported to produce calcium handling defects in subcellular organelles like mitochondria, sarcoplasmic reticulum and sarcolemma. In various cardiovascular diseases,[15] several changes are seen in the diseased myocardium which are associated with oxidative stress and these include elevated levels of inflammatory cytokines as well as reduction in antioxidant enzyme activities and the function of non-enzymatic anti-oxidant systems. The increased oxidative stress then leads to subcellular defects and cardiac dysfunctions through various downstream mechanisms such as lipid peroxidation, proteases activation, myocardial inflammation, inactivation of functional groups, alterations in gene expressions, changes in contractile proteins and mitochondrial calcium overload.[15] Oxidative stress causes changes in the sarcolemma and sarcoplasmic reticulum and induces intracellular calcium overload in cardiomyocytes. It also reduces the activities of Na^+-K^+ ATPase and Na^+-Ca^{2+} exchange systems to further increase the intracellular calcium. In addition, oxidative stress induces changes in the ryanodine receptors (RyR1), in the sarcoplasmic reticulum and makes them leaky for releasing calcium into the cell and producing downstream muscle damage.[57] Prolonged oxidative stress and calcium handling abnormalities produce a loss of calcium sensitivity to myofibrillar ATPase which may cause myofibril degeneration and derangements. Functioning of mitochondria is impaired due to calcium overload whereas oxidative stress induces an increase in mitochondrial ATPase inhibitory factor 1 which worsens the calcium handling.[57] Calcium handling abnormality by the sarcoplasmic reticulum due to oxidative stress has been reported to result in the development of arrhythmias.[15]

It is noteworthy that heart failure is the most prevalent chronic cardiovascular disease which is associated with retention of fluid in the body, peripheral oedema and pulmonary congestion.[58] There are several underlying causes for heart failure and some of these include myocardial infarction, hypertension, cardiomyopathy and valvular heart disease. All these conditions induce structural changes in the heart and lead to impairment of its pumping ability.[58, 59] Blockade of coronary arteries results in reduced blood flow to some areas of the heart leading to cell death and causing myocardial infarction. Although the degree of heart failure due to myocardial infarction is dependent on infarct size, some other factors such as immune activation, inflammation, oxidative stress, changes in mitochondrial bioenergetics and autophagy are considered to be involved in the progression from cardiac hypertrophy to heart failure.[60-62] It is generally believed that an increase in ventricular wall tension as well as oxidative stress lead to cardiac remodelling and subsequent heart failure.[63] Various vasoactive hormones, which are released into circulation upon the blockade of coronary arteries also constrict small vessels in the hypertrophied heart and produce hypoxia for the development of oxidative stress.[64] It is also pointed out that cell death in myocardial infarction is caused by many defects including apoptosis, necrosis, pyroptosis and ferroptosis.[60] These pathways are interrelated but are induced through various factors such as oxidative stress and inflammation. Oxidative stress is considered to play a major role in the pathogenesis of ferroptosis whereas pyroptosis is mainly an inflammation-mediated cell death.[60, 65] Both these pathways of cellular damage involve canonical signalling which is associated with plasma membrane rupture and non-canonical signalling, which is related to

CONTENT

changes in mitochondria or sarcoplasmic reticulum. Oxidative stress has also been observed to mediate insulin resistance through the necroptotic pathway and causes atherosclerotic damage. Some studies have shown that reduction in ROS led to a reduction of oxidative damage and necroptotic cardiomyocyte loss.[60] It is pointed out that hypertrophied hearts have an increased amount of antioxidants, but these are not enough to balance the amount of oxyradicals produced in the hypertrophied heart.[64] ROS oxidise cysteine thiols causing conformational changes that lead to increased release of calcium from the sarcoplasmic reticulum, thus reducing the amount of calcium present inside the sarcoplasmic reticulum; this is responsible for the dysfunctioning of excitation-contraction coupling in cardiomyocytes.[17, 66] Increased oxidative stress and calcium handling abnormalities in cardiomyocytes of the failing heart due to myocardial infarction modify myosin gene expression, decrease ATPase activity of myofibrils and impair the cardiac contractile force development.

Alterations in signalling pathways due to activation of the sympathetic nervous system and renin-angiotensin- aldosterone systems are responsible for the progression of heart failure.[58] Plasma levels of vasoactive hormones such as catecholamines and angiotensin II are increased in pathological conditions and these hormones increase the cardiac muscle mass and produce cardiac hypertrophy for decreasing the ventricular wall tension. However, prolonged exposure of the hypertrophied heart to these vasoactive hormones has been shown to produce calcium handling abnormalities and other subcellular defects for the induction of heart failure.[64] ROS are also responsible for the activation of several signalling kinases and transcription factors in hypertrophied hearts.[67, 68] Furthermore, ROS are known to cause extracellular matrix remodelling by stimulating cardiac fibroblast proliferation and activating matrix metalloproteinases.[69] In fact, the activation of both the sympathetic nervous system and the renin-angiotensin system has been reported to increase the level of oxidative stress which contributes to the progression of heart failure.[70] Failing hearts have also been observed to show an increase in the expression of genes, which code for cytokines and increase the activation of both innate and adaptive immune systems; this observation indicates that inflammation is linked to the development of heart failure.[71]

Pharmacotherapy and intervention strategies for the treatment of cardiovascular disease

Important pathological events in the development of heart failure include elevated levels of vasoactive hormones, activation of the immune system, inflammation, oxidative stress, insulin resistance, formation of toxic substances, alterations in mitochondrial bioenergetics and autophagy.[72-81] These events have thus been considered to be the targets for drug developments and interventions in the treatment of cardiovascular diseases including heart failure. It has been found that blocking of lectin-like oxidised LDL receptor-1 (LOX-1) with an antibody produces inhibition of ROS generation and prevention of mitochondrial damage in heart failure; this is because the binding of ox-LDL to LOX-1 leads to the generation of ROS through activation of a series of downstream reactions.[82, 83] Mitochondria are one of the major producers of endogenous ROS and thus blocking of mitochondrial ROS by using mitoSNO has been observed to prevent cardiac dysfunction.[67] Some natural synthetic antioxidants have been studied for the treatment of cardiovascular diseases. A compound called resveratrol, a natural phytoalexin, has been identified to suppress the high glucose-induced generation of superoxide anion by increasing the phosphorylation of adenosine monophosphate-activated protein kinase. It has also been observed to elicit endothelium-dependent vasodilatations and alleviate endothelial dysfunction due to high glucose levels.[84] However, resveratrol has been reported to have varying levels of effects on cardiometabolic diseases or shows no to very little effect in some other diseases. On the other hand, olive polyphenols like oleuropein and hydroxytyrosol have shown significant results in preclinical trials. Most of the clinical studies have been performed to observe the effects of olive oil for its therapeutic actions on cardiovascular and cardiometabolic health. However, specific studies employing olive phenols as pure compounds have not been performed and thus more research is needed to know about the effects of olive polyphenols. Different preclinical trials in animals have also been carried out to show the therapeutic effects of other natural compounds like quercetin, catechins, curcumin, organosulphur compounds, melatonin, folic acid and glutathione on

CONTENT

cardiometabolic and cardiovascular diseases but well- organised detailed clinical trials are needed to support their effects in humans.[85-87]

Some studies have been conducted to examine synthetic compounds for anti-oxidant properties and their therapeutic effects in cardiovascular diseases. N – acetylcysteine (NAC) has shown some beneficial actions in improving cardiac function in preclinical trials but showed differing effects in various cardiometabolic diseases.[88] Thus, more research is needed to identify the role of NAC as a therapeutic option. Other synthetic compounds include superoxide dismutase mimetics (SOD mimetics) which have shown favourable effects in animal models but there is a lack of clinical studies to indicate their therapeutic use.[89] Probucol is another synthetic compound which has been reported to show significant preclinical and clinical results. Some clinical studies have indicated that probucol may be used as an additive for the treatment of cardiometabolic diseases but further research needs to be performed to examine its long- term benefit and safety.[85, 88, 89] There has been some developments to target mitochondrial abnormalities using small molecules as well as peptides and thus prevent heart failure; these interventions were found to help in mitochondrial detoxification and prevention of heart failure.[90]

Since accumulation of free iron within mitochondria is known to produce an excessive amount of ROS mitochondria- permeable iron chelators like deferiprone has been identified as a new intervention in cardiac disease prevention.[91] Other interventions include anti-oxidative therapies to target oxidative stress in the body by various methods.[92] At present, the best therapy in this regard seems to be the inhibition of xanthine oxidase by allopurinol or oxypurinol.[93, 94] Future antioxidative therapies in heart failure are considered to include increasing endogenous antioxidant capacity and increasing expression of antioxidant- producing enzymes.[92] MicroRNAs are also examined for their ability to act as regulators of endogenous oxidative stress in cardiovascular diseases but their application in humans needs more research.[85] Supplementation with precursors of major cellular antioxidants like GSH and NAD^+ has been shown to increase the endogenous antioxidant capacity.[93, 95] Another approach would be to improve the expression or activity of glutamyl cycle and NAD^+ producers to reduce oxidative stress.[96, 97] The inhibition of necroptotic pathways in cardiomyocytes has also been suggested to reduce cell death.[60] Likewise, various intermediates of the canonical and non-canonical pathways have been targeted by interventions such as protein kinase inhibitors like RIP1kinase inhibitors (necrostatins) and RIP3 inhibitors (GSK'872, HS-1371) for improving cardiac function.[60] In this regard, necrostatin-1 (Nec-1) has been observed to prevent remodelling in acute myocardial infarction as well as, post-myocardial infarction heart failure. It also blocks an enzyme in the inflammatory pathway and thus reduces inflammation- related cell death. Another drug necrosulfonamide, that inhibits MLKL in the canonical pathway has also been reported to depress oxidative stress.[60] Some studies have indicated that the signalling pathways that lead to cell damage under high oxidative stress conditions in right ventricular are different from those in the and left ventricular heart failure and thus further research is needed to incorporate the antioxidant therapy into the heart failure treatment options.[98]

Role of oxidative stress in neurodegenerative diseases

Neurodegenerative diseases occur when the nerve cells or neurons in the brain and spinal cord get damaged and eventually die. The degree of symptoms of neurodegeneration such as memory loss, hallucinations and loss of motor control is considered to depend upon the number of neurons which become damaged during the development of this disorder. These diseases strike in mid to late life and thus the condition of patients is expected to worsen as the population ages.[99] It is pointed out that neurodegenerative disorders affect millions of people all over the world and their rate is increasing for the most common diseases such as Alzheimer's disease and Parkinson's disease. The causes for these diseases are genetic factors, environmental conditions and lifestyle attributes.[100] It is also noteworthy that oxidative stress in the nervous system develops due to the large amounts of ROS and RNS produced by the activated microglia and endothelial cells.[101] The increase in oxidative stress in the nervous system leads to death of neuronal cells by apoptosis and excitotoxicity.[102, 103] RNS however have also been observed to be important biological messengers and thus play critical role in the transmission of signals in the nervous system.[104, 105] Neuronal

CONTENT

damage in some neurodegenerative diseases has also been observed to be due to the activation of glutamate receptors; the excessive activation of these receptors leads to a marked influx of calcium into neurons leading to overstimulation of normal activity and neuronal damage.[106, 107]

It should be emphasised that mitochondria release various apoptotic factors in response to different environmental or internal body signals. These apoptotic factors are also responsible for neuronal cell death in neurodegenerative diseases.[108-110] Excessive oxidative stress can cause mitochondrial DNA damage and genetic mutations which are considered to be associated with neurodegenerative diseases. Genetic aberrations such as single gene disease, proteasome dysfunction and protein misfolding are some conditions which are responsible for neurodegenerative diseases. In addition, complex interactions among multiple predisposing genes have been shown to result in various disease states and worsen the existing neurological disorders.[105, 111] It should also be mentioned that NO is known to play an important role in the transmission of signals throughout the nervous system. It is involved in the regulation and proliferation of vascular smooth muscle cells, leukocyte adhesion, angiogenesis, thrombosis and hemodynamics.[105, 112] Excessive amount of NO leads to the production of reactive nitrogen species in the body and thus can lead to nitrosative stress and neuronal damage. High concentrations of NO are toxic as these combines with tyrosine residues in the body which are needed for proper functioning of the ribonucleoside diphosphate reductase system.[105, 112, 113] Furthermore, several sources of ROS in the nervous system are the excitatory amino acids and neurotransmitters in the brain and neuronal tissue. These amino acids get metabolised and produce ROS which increase oxidative stress. ROS attack glial cells, which maintain homeostasis, protect neurons and form myelin in the nervous system and thus cause neuronal damage.[108, 114]

One of the major neurodegenerative diseases is Alzheimer's disease (AD), which is characterised by abnormal deposition of amyloid beta peptide especially in the hippocampus. The intracellular accumulation of neurofibrillary tangles and hyperphosphorylated T proteins result in the loss of synapses and dendritic spines, as well as hypoperfusion and hyperaemia. The oligomeric amyloid beta peptide is responsible for the symptoms seen in AD and also serves as the diagnostic criteria of this diseases upon the estimation of oxidative stress.[115-117] Mitochondrial defects also play an essential role in the neuron degeneration in AD by generating excessive amounts of ROS, activating mitochondrial permeability transition pores, excitotoxicity, impaired production of adenosine triphosphate and altered homeostasis of calcium.[118-119] Since metal ions like copper and iron play some critical roles in the production of neurodegenerative diseases, iron has been observed to react with hydrogen peroxide and generate ROS in lysosomes to cause oxidative damage.[120] The presence of increased levels of redox- active iron has also been observed to trigger amyloid plaque formation. Another pathway by which iron generates oxidative stress is ferroptosis which has been identified as the major cause of neuronal cell death in neurodegenerative diseases. Ferroptosis refers to programmed cell death which is caused by accumulation of lipid peroxides in the cell.[121-123] Loosely bound metal ions like copper act as catalysts for the production of ROS and in fact an increase in the amount of loose copper ions has been detected in AD. Copper ions bound to amyloid plaques have also been demonstrated to contribute to oxidative stress.[124-126] It may be noted that increased oxidative stress in the neuronal cells has been reported to oxidise some proteins and reduce the activities of enzymes like creatine kinase, glutamine synthetase and glutamine synthase in AD.[118, 127, 128] Oxidation of proteins is also responsible for the hyperphosphorylation of T proteins through microtubule-associated protein kinase pathway and activation of transcription factor nuclear factor. This thus leads to formation of neurofibrillary tangles which are one of the major characteristics of AD.[105, 129]

Pharmacotherapy and intervention strategies in treatment of neurodegeneration

Antioxidant therapies are one of the major areas of research in the treatment for neurodegenerative diseases and thus several studies have discussed the mechanisms and identification of targets for preventing the impact of oxidative stress in inducing neurodegeneration.[130-142] Therapeutic

CONTENT

options for upstream oxidative stress include enzymes and antioxidants to reduce the generation of free radicals and interrupt the interaction between neuronal protein and oxidative stress.[143, 144] Downstream antioxidant therapy in neuronal disorders due to oxidative stress includes preventing neuronal inflammation and scavenging the free radicals produced.[144-146] The use of antioxidants to prevent oxidative damage caused by Fenton-like reactions involving iron is also considered to be a therapeutic intervention.[121] G- protein coupled receptors (GPCR) are the largest family of transmembrane receptors and have been observed to be involved in the pathology of many neurodegenerative diseases. Allosteric modulators of GPCR and neuropeptides have also been used for the treatment of neurodegenerative diseases.[147, 148] A study has also been observed to minimise plaque production in AD by genetic deletion of mGluR5 receptor which belongs to the GPCR family.[149] Targeting of serotonergic receptors such as serotonin- 6 receptor ($5\text{-}HT_6R$) has also been identified as an intervention for the treatment of AD.[150, 151] Other types of intervention strategies include the use of iron chelators such as deferiprone which targets iron metabolism.[152]

Currently used treatment of AD is based on cholinergic hypothesis, according to which deficiency of acetylcholine (ACh) is observed in the central nervous system in patients suffering from this disease. Thus, the current approach is the cholinergic replacement strategy which was attempted to use muscarinic and nicotinic cholinergic ligands and acetylcholinesterase inhibitors.[153, 154] Other treatments used are dual-binding site AChE inhibitors, dual-binding AChE and BACE-1 inhibitors and AChE inhibitors and calcium channel blockers. Non-AChE directed multitarget drug developments and multitarget bioavailable metal chelators are also under study in the treatment of AD.[154] Some examples of drugs in use for the treatment of AD include aducanumab and tacrine. Aducanumab is a human monoclonal antibody which has been observed to enter the brain, bind to parenchyma beta plaques and reduce soluble and insoluble amyloid beta plaques in a dose-dependent manner in AD.[155, 156] Tacrine is a non-selective AChE inhibitor and was the first approved drug for AD. It is however no longer in use because it was observed to have some adverse effects and dose-dependent hepatotoxicity. A derivative of tacrine called HLS-3 has been found to show similar central effects and lesser peripheral adverse effects as compared to oral tacrine.[157-159]

Role of oxidative stress in some cancers

Cancer is rising worldwide as it caused approximately 10 million deaths in 2020.[160] According to WHO, 18.08 million cases of cancer were diagnosed with cancers of lung, breast and prostate being the most frequent; lung cancer in men and breast cancer in women are most frequently diagnosed. The most deadly cancers are of lung, liver and stomach and these are the most common cause of mortality for men. In women, breast cancer has the highest rate of mortality followed by lung and stomach cancers. It has been estimated that the mortality rate of cancer will become greater than the mortality rate of ischaemic heart disease by 2060.[161] Common causes of cancer are tobacco use, high body mass index, alcoholism and sedentary lifestyle. Cancer can also be caused by some infections like hepatitis and human papillomavirus (HPV) which account for about 30 % of cancer cases in low and lower-middle income nations.[160]

ROS have been identified to have distinct effects on cellular components and have both pro-tumorigenic and antitumorigenic effects.[162] Since ROS are involved in normal cell metabolism and cell signalling as well as ageing and diseases due to irreversible damage to lipids, DNA and proteins,[163] ROS have been observed to promote proliferation and survival of cancer cells, angiogenesis and metastasis in mouse cell models and human cell lines.[162, 164, 165] ROS also activate stress-induced signalling pathways that can induce cell cycle arrest, senescence and cancer cell death.[164] Autophagy helps to maintain genomic stability not only by suppressing chronic tissue damage but may also promote tumour growth by suppression of p53 response which prevents the diversion of tumours to benign oncocytomas.[163-166] Autophagy removes damaged organelles like mitochondria and limits ROS amplification.[167-169] Increased levels of ROS have been shown to cause oxidation of guanine and irreversible cysteine modification in addition to acting as carcinogenic and promoting genomic instability.[164-170] Environmental carcinogens such as cigarette smoke have been observed to have very high amounts of ROS which are involved in cells mediated by oncogenes or loss of tumour suppressors as is seen in the downregulation of p53.[163] ROS are also believed to promote tumour through the activation of mitogenic

CONTENT

signalling pathways like PI3K/AKT/mTOR and MAPK/ERK signalling cascades.[171-173] ROS have been reported to be involved in the loss of cell-to-cell adhesion due to which the tumour cells break through the cell basement membrane and cause metastasis.[164-174] Endogenous oxidants have been shown to prevent initiation of tumour; GPX3 suppresses tumour initiation in mouse models of colon cancer,[175] SOD gets localised to mitochondria and block cancer cell proliferation[176] and peroxiredoxin inhibits cancer cell growth.[177] Exogenous antioxidants such as N-acetyl cysteine, vitamin E[178] and vitamin C have also been observed to have antitumour as well as some tumour proliferating effects.[179] Amino acids were shown to regulate ROS balance in cancer cells and act as protective factors against cancers. Glutamate and methionine were demonstrated to modify levels of NADPH in cancer cells and helped to maintain ROS levels below the toxic threshold along with cysteine which has strong antioxidant properties.[180-182] Some genetic alterations like ectopic expression of oncogenes Ras,[183] loss of tumour suppressor p53[184] and genetic ablation of the gene encoding breast cancer (*Brca1*)[185] have been observed to increase ROS levels and induce tumorigenesis. These observations suggest that the development of oxidative stress plays a critical role in the genesis of some types of cancer.

Pharmacotherapy and intervention strategies for the treatment of cancer

Since ROS are the major cause of cancer progression, many treatments target ROS to prevent the development of cancer. Several natural antioxidants and phytochemicals have been introduced as anti-cancer therapies as they have anti-proliferative and pro-apoptotic effects.[186, 187] However, there are studies which have indicated that targeting ROS by antioxidants to reach normal cell concentrations for destroying tumours presents many problems which need to be addressed.[180] Cancer cells are known to thrive on ROS levels which are moderately higher than those in normal cells. Thus, therapeutic strategies are being developed to elevate ROS levels that do not exceed the redox adaptation of the cell and induce oxidative stress which is incompatible with cellular life.[188] In order to increase ROS levels and cause cell death, motexafin, gadolinium and anthracyclins have been used in cancerous cells.[189, 190] Antioxidant product inhibition can be achieved by depletion of GSH activity as is seen in the case of buthionine sulfoximine which inhibits GSH synthesis.[191] Imexon is used in the treatment of advanced stages of cancer as it disrupts GSH activity by binding to the thiol functional group of reduced GSH and thus depletes the GSH pool for antioxidant activity.[192, 193]

There are studies targeting cysteine metabolism and ferroptosis to limit tumour growth; however, there are many cancer cell lines which show resistance to this treatment and thus it is important to develop efficient drug-targeting methods.[180, 194, 195] Another therapeutic method is nanomedicine which involves many biocompatible and biodegradable systems that deliver conventional chemotherapeutic drugs in the body. These interventions help to increase the availability of drugs around the tumour tissue and improve their release. Nanoparticles have also been used in the diagnosis as well as treatment of cancer.[186, 196] Targeted therapy helps to modulate the specific site like tumour vasculature or intracellular organelles and leave the surroundings unaffected. This would help to make the treatment of cancer more specific and reduce the drawbacks of the treatment.[197] Gene therapy and expression of genes which trigger apoptosis and wild-type tumour suppressors are also considered to be good interventions and thus have been investigated.[198] Thermal ablation of tumours and magnetic hyperthermia are considered to be tools for precise medication and serve as substitutes for more invasive options like surgery.[199] Some fields still under study include targeted silencing mediated by siRNAa, radiomics and pathomics.[186] Phytochemicals which are secondary plant metabolites have been observed to potentiate the efficiency of chemotherapeutic agents by exacerbating oxidative stress in cancer cells.[200] Thus, these are the basis for the development of novel interventions for the protection and treatment of cancer.

CONTENT

Conclusion

Change in the diet and unhealthy lifestyle have been a major cause of cardiovascular diseases, neurodegenerative diseases and cancer. The excessive production of ROS and the presence of excessive amounts of AGEs in modern diets cause an increase in the oxidative stress that leads to many chronic diseases, three of which were discussed in this review. There are commonalities among the pathogenic factors like ROS, AGE and NO that may cause these diseases. All these factors when present in excess create abnormalities in the metabolic pathways of the body by inducing an increased oxidative stress which further leads to many other problems like inflammation in the body organs as well as causing DNA damage or lipid deposition. The increased levels of ROS and AGEs result in activation of the immune system that leads to inflammation, which is also a common factor in these chronic diseases. The preventive strategies for all the three diseases include following a healthy lifestyle with moderate exercise and also intake of nutritious foods rich in antioxidants such as fresh fruits and vegetables. Antioxidants such as vitamins A, C and E; beta-carotenes and bioflavonoids are helpful in the reduction of oxidative stress. Consumption of foods rich in calories and high content of AGEs should be reduced as a common preventive strategy for cardiovascular and neurodegenerative diseases as well as cancer. Development of prevention strategies based on natural food resources and traditional medicines should be encouraged to prevent the occurrence of many chronic diseases. In addition, it is of great importance to develop more effective antioxidants with anti-inflammatory activities and other interventions for some combination therapies, if we have to improve the outcome of patients with chronic diseases.

Ethics

This study was a secondary analysis and did not directly involve with human participants or experimental animals. Therefore, the ethics approval was not required in this paper.

Acknowledgement

The infrastructure support for the preparation of this article was provided by the St. Boniface Hospital Albrechtsen Research Centre. Thanks are due to Ms Khushman Kaur for her help in preparing the manuscript.

Conflicts of interest

The authors declare that there is no conflict of interest.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Data access

The data that support the findings of this study are available from the corresponding author upon reasonable individual request.

Author ORCID numbers

Jasneet K Tiwana (JKT):
0009-0008-7168-926X
Anureet K Shah (AKS):
0000-0003-1765-0942
Naranjan S Dhalla (NSD):
0000-0002-4894-4727

Author contributions

Conceptualisation: NSD
Validation: AKS
Data curation: JKT
Writing - original draft: JKT
Writing - review and editing: AKS, NSD

CONTENT

References

1. Bernell S, Howard SW. Use your words carefully: What is a chronic disease? Front Public Health. 2016;4:159. doi: 10.3389/fpubh.2016.00159.
2. Jones R. Acute and chronic illness. Br J Gen Pract. 2010;60(579):714. doi: 10.3399/bjgp10X515638.
3. Martin CM. Chronic disease and illness care: adding principles of family medicine to address ongoing health system redesign. Can Fam Physician. 2007 Dec;53(12):2086-91. PMID: 18077734.
4. World Health Organization [Internet]. Cardiovascular diseases. [Cited: 10-Jan-2024]. Available at: https://www.who.int/health-topics/cardiovascular-diseases#tab=tab_1.
5. Gracey M, King M. Indigenous health part 1: determinants and disease patterns. Lancet. 2009;374(9683):65-75. doi: 10.1016/S0140-6736(09)60914-4.
6. Phillips KM, Pehrsson PR, Agnew WW, Scheett AJ, Follett JR, Lukaski HC, et al. Nutrient composition of selected traditional United States Northern Plains Native American plant foods. J Food Comp Anal. 2014;34(2):136-52. doi: 10.1016/j.jfca.2014.02.010.
7. Park S, Hongu N, Daily JW. Native American foods: History, culture, and influence on modern diets. J Ethnic Foods. 2016;3(3):171-7. doi: 10.1016/j.jef.2016.08.001.
8. Vanderhoof JA. Immunonutrition: the role of carbohydrates. Nutrition. 1998;14(7-8):595-8. doi: 10.1016/s0899-9007(98)00006-9.
9. Meetoo D. Chronic diseases: the silent global epidemic. British Nursing. 2013;17:21. doi: 10.12968/bjon.2008.17.21.31731.
10. Cockerham WC, Hamby BW Oates GR. The social determinants of chronic disease. Am J Prev Med. 2017;52(1S1):S5-S12. doi: 10.1016/j.amepre.2016.09.010.
11. Hajat C, Stein E. The global burden of multiple chronic conditions: A narrative review. Prev Med Rep. 2018;12:284-93. doi: 10.1016/j.pmedr.2018.10.008.
12. Mittal M, Siddiqui MR, Tran K, Reddy SP, Malik AB. Reactive oxygen species in inflammation and tissue injury. Antioxid Redox Signal. 2014;20(7):1126-67. doi: 10.1089/ars.2012.5149.
13. Weidinger A, Kozlov AV. Biological activities of reactive oxygen and nitrogen species: oxidative stress versus signal transduction. Biomolecules. 2015;5(2):472-84. doi: 10.3390/biom5020472.
14. Li W, Young JF, Sun J. NADPH oxidase-generated reactive oxygen species in mature follicles are essential for Drosophila ovulation. Proc Natl Acad Sci USA. 2018;115(30):7765-70. doi: 10.1073/pnas.1800115115.
15. Dhalla NS, Elimban V, Bartekova M, Adameova A. Involvement of oxidative stress in the development of subcellular defects and heart disease. Biomedicines. 2022;10(2):393. doi: 10.3390/biomedicines10020393.
16. Bhattacharyya A, Chattopadhyay R, Mitra S, Crowe SE. Oxidative stress: An essential factor in the pathogenesis of gastrointestinal mucosal diseases. Physiol Rev. 2014;94(2):329-54. doi: 10.1152/physrev.00040.2012.
17. Ushio-Fukai M. Vascular signaling through G protein coupled receptors – new concepts. Curr Opin Nephrol Hypertens. 2010;18(2):153-9. doi: 10.1097/MNH.0b013e3283252efe.
18. Zorov DB, Juhaszova M, Sollott SJ. Mitochondrial reactive oxygen species (ROS) and ROS-induced ROS release. Physiol Rev. 2014;94(3):909-50. doi: 10.1152/physrev.00026.2013.
19. Grivennikova VG, Vinogradov AD. Mitochondrial production of reactive oxygen species. Biochemistry. 2013;78(13):1490-511. doi: 10.1134/S0006297913130087.
20. Venditti P, Stefano LD, Meo SD. Mitochondrial metabolism of reactive oxygen species. Mitochondrion. 2013;13(2):71-82. doi: 10.1016/j.mito.2013.01.008.
21. Shkolnik K, Tadmor A, Ben-Dor S, Dekel N. Reactive oxygen species are indispensable in ovulation. Proc Natl Acad Sci USA. 2011;108(40):1462-7. doi: 10.1073/pnas.1017213108.
22. Yarosz EL, Chang CH. The role of reactive oxygen species in regulating T cell mediated immunity and disease. Immune Network. 2018;18(1):e14. doi: 10.4110/in.2018.18.e14.
23. Eze M. The oxygen paradox and the place of oxygen in our understanding of life, aging, and death. Ultim Real Mean. 2006;29(1):46-61. doi: 10.3138/uram.29.1-2.46.
24. Magder S. Reactive oxygen species: toxic molecules or spark of life? Crit Care. 2006;10(1):208. doi: 10.1186/cc3992.
25. Choe E, Min DB. Chemistry and reactions of reactive oxygen species in foods. Crit Rev Food Sci Nutr. 2006;46(1):1-22. doi: 10.1080/10408390500455474.
26. World Health Organization [Internet]. Cardiovascular diseases factsheet. 2021. [Cited: 10-Jan-2024]. Available at: https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds).
27. Churchyard G, Kim P, Shah NS, Rustomjee R, Gandhi N, Mathema B, et al. What we know about tuberculosis transmission: An overview. J Infect Dis. 2017;216(suppl_6):S629-S635. doi: 10.1093/infdis/jix362.
28. Uribarri J, Woodruff S, Goodman S, Weijing C, Chen X, Pyzik R, et al. Advanced glycation end product in foods and a practical guide to their reduction in the diet. J Am Diet Assoc. 2010;110(6):911-6.e12. doi: 10.1016/j.jada.2010.03.018.
29. Aragno M, Mastrocola R. Dietary sugars and endogenous formation of advanced glycation end products: Emerging mechanisms of disease. Nutrients. 2017;9(4):385. doi: 10.3390/nu9040385.
30. Valko M, Jomova K, Rhodes CJ, Kuca K, Musilek K. Redox- and non-redox-metal induced formation of free radicals and their role in human disease. Arch Toxicol. 2016;90(1):1-37. doi: 10.1007/s00204-015-1579-5.
31. Titheradge, M. Nitric oxide in septic shock. Biochem Biophys Res Commun. 1999;1411(2-3):437-55. doi: 10.1016/s0005-2728(99)00031-6.
32. Uribarri J, Cai W, Sandu O, Peppa M, Goldberg T, Vlassara H. Diet-derived advanced glycation end products are major contributors to the body's AGE pool and induce inflammation in healthy subjects. Ann N Y Acad Sci. 2005;1043:461-6. doi: 10.1196/annals.1333.052.
33. Rajopadhye SH, Mukherjee SR, Chowdhary AS, Dandekar SP. Oxidative stress markers in tuberculosis and HIV/TB co-infection. J Clin Diagn Res. 2017;11(8):BC24-BC28. doi: 10.7860/JCDR/2017/28478.10473.

CONTENT

34. Hibbs J, Taintor R, Vavrin Z, Rachlin E. Nitric oxide: A cytotoxic activated macrophage effector molecule. Biochem Biophys Res Commun. 1988;157(1):87-94. doi: 10.1016/s0006-291x(88)80015-9.
35. Pacher P, Beckman J, Liaudet L. Nitric oxide and peroxynitrite in health and disease. Am Physiol Soc. 2007;87(1):315-424. doi: 10.1152/physrev.00029.2006.
36. Korge P, Calmettes G, Weiss JN. Increased reactive oxygen species production during reductive stress: The roles of mitochondrial glutathione and thioredoxin reductases. BBA Bioenergetics. 2015;1847(6-7):514-25. doi: 10.1016/j.bbabio.2015.02.012.
37. Frak W, Wojtasinska A, Lisinska W, Mlynarska E, Franczyk B, Rysz J. Pathophysiology of cardiovascular diseases: New insights into molecular mechanisms of atherosclerosis, arterial hypertension, and coronary artery disease. Biomedicines. 2022;10(8):1938. doi: 10.3390/biomedicines10081938.
38. Thiriet M. Cardiovascular disease: An introduction. Vasculopathies. 2018;8:1-90. doi: 10.1007/978-3-319-89315-0_1.
39. Mendis S, Puska P, Norrving, B, World Health Organization, World Heart Federation. et al. Global atlas on cardiovascular disease prevention and control. Geneva, Switzerland: World Health Organization, 2011.
40. Mackinnon ES, Goeree R, Goodman SG, Rogoza RM, Packalen M, Pericleous L, et al. Increasing prevalence and incidence of atherosclerotic cardiovascular disease in adult patients in Ontario, Canada from 2002 to 2018. Can J Cardiol Open. 2022;4(2):206-13. doi: 10.1016/j.cjco.2021.10.003.
41. Stewart J, Manmathan G, Wilkinson P. Primary prevention of cardiovascular disease: A review of contemporary guidance and literature. JRSM Cardiovasc Dis 2017;6:1-9. doi: 10.1177/2048004016687211.
42. Nagase M, Ayuzawa N, Kawarazaki W, Ishizawa K, Ueda K, Yoshida S, Fujita T. Oxidative stress causes mineralocorticoid receptor activation in rat cardiomyocytes: role of small GTPase Rac1. Hypertension. 2012;59(2):500-6. doi: 10.1161/HYPERTENSIONAHA.111.185520.
43. Ouvrard-Pascaud A, Sainte-Marie Y, Benitah JP, Perrier R, Soukaseum C, Cat AN, et al. Conditional mineralocorticoid receptor expression in the heart leads to life threatening arrhythmias. Circulation. 2005;111(23):3025-33. doi: 10.1161/CIRCULATIONAHA.104.503706.
44. Oakley RH, Cruz-Topete D, He B, Foley JF, Myers PH, Xu X, et al. Cardiomyocyte glucocorticoid and mineralocorticoid receptors directly and antagonistically regulate heart disease in mice. Sci Signal. 2019; 12(577):1-38. doi: 10.1126/scisignal.aau9685.
45. Buonafine M, Bonnard B, Jaisser F. Mineralocorticoid receptor and cardiovascular disease. Am J Hypertens. 2018;31(11):1165-74. doi: 10.1093/ajh/hpy120.
46. Ayuzawa N, Nigase M, Ueda K, Nishimoto M, Kawarazaki W, Marumo T, et al. Rac1mediated activation of mineralocorticoid receptor in pressure overload-induced cardiac injury. Hypertension. 2016;67(1):99-106. doi: 10.1161/HYPERTENSIONAHA.115.06054
47. Kuroda J, Ago T, Matsushima S, Zhai P, Schneider MD, Sadoshima J. NADPH oxidase 4 (Nox4) is a major source of oxidative stress in the failing heart. Proc Natl Acad Sci USA. 2010;107(35):15565-70. doi: 10.1073/pnas.1002178107.
48. Shibata S, Nagase M, Yoshida S, Kawarazaki W, Kurihara H, Tanaka H, et al. Modification of mineralocorticoid receptor function by Rac1 GTPase: implications in proteinuric kidney disease. Nature Med. 2008;14:1370-6. doi: /10.1038/nm.1879.
49. Okamoto K, Tanaka H, Ogawa H, Makino Y, Eguchi H, Hayashi S, et al. Redox dependent regulation of nuclear import of the glucocorticoid receptor. J Biol Chem. 1999;274(15):10363-71. doi: 10.1074/jbc.274.15.10363.
50. Mohamed R, Janke R, Guo W, Cao Y, Zhou Y, Zheng W, et al. GPCR transactivation signalling in vascular smooth muscle cells: role of NADPH oxidases and reactive oxygen species. Vasc Biol. 2019;1(1):R1-R11. doi: 10.1530/VB-18-0004.
51. Ushio-Fukai M, Griendling KK, Becker PL, Hilenski L, Halleran S, Alexander RW. Epidermal growth factor receptor transactivation by angiotensin II requires reactive oxygen species in vascular smooth muscle cells. Arterioscler Thromb Vasc Biol. 2001;21(4):489-95. doi: 10.1161/01.atv.21.4.489.
52. Wu X, Tu X, Joeng KS, Hilton MJ, Williams DA, Long F. Rac1 activation controls nuclear localization of b-catenin during canonical wnt signaling. Cell. 2008;133(2):340-53. doi: 10.1016/j.cell.2008.01.052.
53. Kawashima T, Bao YC, Nomura Y, Moon Y, Tonozuka Y, Minoshima Y, et al. Rac1 and a GTPase-activating protein, MgcRacGAP, are required for nuclear translocation of STAT transcription factors. J Cell Biol. 2006;175(6):937-46. doi: 10.1083/jcb.200604073.
54. Berridge MJ. The inositol triphosphate/calcium signaling pathway in health and disease. Physiol Rev. 2016;96(4):1261-96. doi: 10.1152/physrev.00006.2016.
55. Fanelli C, Zatz R. Linking oxidative stress, the renin-angiotensin system, and hypertension. Hypertension. 2011;57: 373-4. doi: 10.1161/HYPERTENSIONAHA.110.167775.
56. Callera GE, Montezano AC, Yogi A, Tostes RC, Touyz RM. Vascular signaling through cholesterol-rich domains: implications in hypertension. Curr Opin Nephrol Hypertens. 2007;16(2):90-104. doi: 10.1097/MNH.0b013e328040bfbd.
57. Anderson DC, Betzenhauser MJ, Reiken S, Meli AC, Umanskaya A, Xie W, et al. Ryanodine receptos oxidation causes intracellular calcium leak and muscle weakness in aging. Cell Metab. 2011;14(2):196-207. doi: 10.1016/j.cmet.2011.05.014.
58. Moris D, Spartalis M, Spartalis E, Karachaliou GS, Karaolanis GI, Tsourouflis G, et al. The role of reactive oxygen species in the pathophysiology of cardiovascular diseases and clinical significance of myocardial redox. Ann Transl Med. 2017;5(16):326. doi: 10.21037/atm.2017.06.27.
59. Kim H, Yun J, Kwon SM, Pineda B. Therapeutic strategies for oxidative stress-related cardiovascular diseases removal of excess reactive oxygen species in adult stem cells. Oxid Med Cell Longev. 2016:2483163. doi: 10.1155/2016/2483163.
60. Adameova A, Horvath C, Abdul-Ghani S, Varga ZV, Suleiman MS, Dhalla NS. Interplay of oxidative stress and

CONTENT

necrosis-like cell death in cardiac ischemia/reperfusion injury: A focus on necroptosis. Biomedicines. 2022;10(1):127. doi: 10.3390/biomedicines10010127.
61. Ray PD, Huang BW, Tsuji Y. Reactive oxygen species (ROS) homeostasis and redox regulation in cellular signaling. Cell Signal. 2012;24(5):981-90. doi: 10.1016/j.cellsig.2012.01.008.
62. Tsutsui H, Kinugawa S, Matsushima S. Oxidative stress and heart failure. Am J Physiol Heart Circ Physiol. 2011;301(6):H2181-90. doi: 10.1152/ajpheart.00554.2011.
63. Kaludercic N, Carpi A, Menabo R, Lisa FD, Paolocci N. Monoamine oxidases (MAO) in the pathogenesis of heart failure and ischemia/reperfusion injury. Biochim Biophys Acta. 2011;1813(7):1323-32. doi: 10.1016/j.bbamcr.2010.09.010.
64. Shah AK, Bhullar SK, Elimban V, Dhalla NS. Oxidative stress as a mechanism for functional alterations in cardiac hypertrophy and heart failure. Antioxidants. 2021;10(6):931. doi: 10.3390/antiox10060931.
65. Fang X, Wang H, han D, Xie E, Yang X, Wei J, Gu S, et al. Ferroptosis as a target for protection against cardiomyopathy. Proc Natl Acad Sci USA. 2019;116(7):2672-80. doi: 10.1073/pnas.1821022116.
66. Tsutsui H, Tsuchihashi-Makaya M, Kinugawa S, Goto D, Takeshita A, JCAREGENERAL investigators. Characteristics and outcomes of patients with heart failure in general practices and hospitals. Circ J. 2007;71(4):449-54. doi: 10.1253/circj.71.449.
67. Ayoub KF, Pothineni NVK, Rutland J, Ding Z, Mehta JL. Immunity, inflammation, and oxidative stress in heart failure: Emerging molecular targets. Cardiovasc Drugs Ther. 2017;31(5-6):593-608. doi: 10.1007/s10557-017-6752-z.
68. Schenkel PC, Tavares AMV, Fernandes RO, Diniz GP, Bertagnolli M, Araujo ASR, et al. Redox-sensitive prosurvival and proapoptotic protein expression in the myocardial remodeling post-infarction in rats. Mol Cell Biochem. 2010;341(12):1–8. doi: 10.1007/s11010-010-0431-8.
69. Terentyev D, Gyorke I, Belevych AE, Terentyeva R, Sridhar A, Nishijima, et al. Redox modification of ryanodine receptors contributes to sarcoplasmic reticulum Ca2+ leak in chronic heart failure. Circ Res. 2008;103(12):1466-72. doi: 10.1161/CIRCRESAHA.108.184457.
70. Sabri A, Hughie HH, Lucchesi PA. Regulation of hypertrophic and apoptotic signaling pathways by reactive oxygen species in cardiac myocytes. Antiox Redox Signal. 2003;5(6):731-40. doi: 10.1089/152308603770380034.
71. Cesselli D, Jakoniuk I, Barlucchi L, Beltrami AP, Hintze TH, Nadal-Ginard B, et al. Oxidative stress–mediated cardiac cell death is a major determinant of ventricular dysfunction and failure in dog dilated cardiomyopathy. Circ Res. 2001;89(3):279-86. doi: 10.1161/hh1501.094115.
72. Dhalla NS, Temsah RM, Netticadan T. Role of oxidative stress in cardiovascular diseases. J Hypertens. 2000;18(6):655-73. doi: 10.1097/00004872-200018060-00002.
73. Bartekova M, Radosinska J, Jelemensky M, Dhalla NS. Role of cytokines and inflammation in heart failure during health and disease. Heart Fail Rev. 2018;23:733-58. doi: 10.1007/s10741-018-9716-x.
74. Prasad K. Is there any evidence that AGEs/RAGE is a universal biomarker/risk marker for diseases? Mol Cell Biochem. 2019;451(1-2):139-44. doi: 10.1007/s11010-018-3400-2.
75. Abdelgadir E, Ali R, Rashid F, Bashier A. Effect of metformin on different non-diabetes related conditions, a special focus on malignant conditions: Review of literature. J Clin Med Res. 2017;9(5):388-95. doi: 10.14740/jocmr2922e.
76. Lv Z, Guo Y. Metformin and its benefits for various diseases. Front Endocrinol (Lausanne). 2020;11:191. doi: 10.3389/fendo.2020.00191.
77. Aimo A, Castiglione V, Borrelli C, Saccaro LF, Franzini M, Masi S, Emdin M, Giannoni A. Oxidative stress and inflammation in the evolution of heart failure: From pathophysiology to therapeutic strategies. Eur J Prev Cardiol. 2020;27(5):494-510. doi: 10.1177/2047487319870344.
78. Tomandlova M, Parenica J, Lokaj P, Ondrus T, Kala P, Miklikova M, et al. Prognostic value of oxidative stress in patients with acute myocardial infarction complicated by cardiogenic shock: A prospective cohort study. Free Radic Biol Med. 2021;174:66-72. doi: 10.1016/j.freeradbiomed.2021.07.040.
79. Mongirdienė A, Liuizė A, Karčiauskaitė D, Mazgelytė E, Liekis A, Sadauskienė I. Relationship between oxidative stress and left ventricle markers in patients with chronic heart failure. Cells. 2023;12(5):803. doi: 10.3390/cells12050803.
80. Bhullar SK, Shah AK, Dhalla NS. Role of angiotensin II in the development of subcellular remodeling in heart failure. Explor Med. 2021;2:352–71. doi: 10.37349/emed.2021.00054.
81. Bhullar SK, Shah AK, Dhalla NS. Mechanisms for the development of heart failure and improvement of cardiac function by angiotensin-converting enzyme inhibitors. Scr Med. 2022;53(1):51-76. doi: 10.5937/scriptamed53-36256.
82. Spinale FG, Coker ML, Thomas CV, Walker JD, Mukherjee R, Hebbar L. Time dependent changes in matrix metalloproteinase activity and expression during the progression of congestive heart failure. Circulation Res. 1998;82(4):482-95. doi: 10.1161/01.res.82.4.482.
83. D'Oria R, Schipani R, Leonardini A, Natalicchio A, Perrini S, Cignarelli A, et al. The role of oxidative stress in cardiac disease: From physiological response to injury factor. Oxid Med Cell Longev. 2020;1-29. doi: 10.1155/2020/5732956.
84. Sugimoto K, Ishibashi T, Sawamura T, Inoue N, Kamioka M, Uekita H, et al. LOX-1MT1-MMP axis is crucial for RhoA and Rac1 activation induced by oxidized low-density lipoprotein in endothelial cells. Cardiovasc Res. 2009;84(1):127-36. doi: 10.1093/cvr/cvp177.
85. Bartekova M, Adameova A, Gorbe A, Ferenczyova K, Pechanova O, Lazou A, et al. Natural and synthetic antioxidants targeting cardiac oxidative stress and redox signaling in cardiometabolic diseases. Free Radic Biol Med. 2021;169:446-77. doi: 10.1016/j.freeradbiomed.2021.03.045.
86. Papakyriakopoulou P, Velidakis N, Khattab E, Valsami G, Korakianitis I, Kadoglou NPE. Potential pharmaceutical applications of quercetin in cardiovascular diseases. Pharmaceuticals. 2022;15(8):1019. doi: 10.3390/ph15081019.

CONTENT

87. Mehmood A, Usman M, Patil P, Zhao L, Wang C. A review on management of cardiovascular diseases by olive polyphenols. Food Sci Nutr. 2020;8(9):4639-55. doi: 10.1002/fsn3.1668.
88. Khan SA, Campbell AM, Lu Y, An L. Alpert JS, Chen QM. N-acetylcysteine for cardiac protection during coronary artery reperfusion: A systematic review and meta-analysis of randomized control trials. Front Cardiovasc Med. 2021;8:752939. doi: 10.3389/fcvm.2021.752939.
89. Maksimenko AV, Vavaev AV. Antioxidant enzymes as potential targets in cardioprotection and treatment of cardiovascular diseases. Enzyme antioxidants: the next stage of pharmacological counterwork to the oxidative stress. Heart Int. 2012;7(1):e3. doi: 10.4081/hi.2012.e3.
90. Ding Z, Liu S, Wang X, Khaidakov M, Dai Y, Mehta JL. Oxidant stress in mitochondrial DNA damage, autophagy and inflammation in atherosclerosis. Sci Rep. 2013;3:1077. doi: 10.1038/srep01077.
91. Methner C, Chouchani ET, Buonincontri G, Pell VR, Sawiak SJ, Murphy MP, Kreig T. Mitochondria selective S-nitrosation by mitochondria-targeted S-nitrosothiol protects against post-infarct heart failure in mouse hearts. Eur J Heart Fail. 2014;16(7):712-7. doi: 10.1002/ejhf.100.
92. Xu Q, Hao X, Yang Q, Si L. Resveratrol prevents hyperglycemia-induced endothelial dysfunction via activation of adenosine monophosphate-activated protein kinase. Biochem Biophys Res Commun. 2009;388(2):389-94. doi: 10.1016/j.bbrc.2009.08.021.
93. Pol AV, Gilst WH, Voors AA, Meer PV. Treating oxidative stress in heart failure: past, present and future. Eur J Heart Fail. 2019;21(4):425-35. doi: 10.1002/ejhf.1320.
94. Bendova P, Mackova E, Haskova P, Vavrova A, Jirkovsky E, Sterba M. Comparison of clinically used and experimental iron chelators for protection against oxidative stress-induced cellular injury. Chem Res Toxicol. 2010;23(6):1105-14. doi: 10.1021/tx100125t.
95. Cingolani HE, Plastino JA, Escudero EM, Mangal B, Brown J, Perez NG. The effect of xanthine oxidase inhibition upon ejection fraction in heart failure patients: La Plata study. J Card Fail. 2006;12(7):491-8. doi: 10.1016/j.cardfail.2006.05.005.
96. Freudenberger RS, Schwarz Jr RP, Brown J, Moore A, Mann D, Givertz MM, et al. Rationale, design and organisation of an efficacy and safety study of oxypurinol Added to standard therapy in patients with NYHA class III – IV congestive heart failure. Expert Opin Investig Drugs. 2004;13(11):1509-16. doi: 10.1517/13543784.13.11.1509.
97. Townsend DM, Tew KD, Tapiero H. The importance of glutathione in human disease. Biomed Pharmacotherapy. 2003;57(3-4):145-55. doi: 10.1016/s0753-3322(03)00043-x.
98. Kovacs A, Herwig M, Budde H, Delalat S, Kolijn D, Bodi B, et al. Interventricular differences of signaling pathways-mediated regulation of cardiomyocyte function in response to high oxidative stress in the post-ischemic failing rat heart. Antioxidants (Basel). 2021;10(6):964. doi: 10.3390/antiox10060964.
99. Adamy C, Mulder P, Khouzami L, Andrieu-abadie N, Defer N, Candiani G, et al. Neutral sphingomyelinase inhibition participates to the benefits of N-acetylcysteine treatment in post-myocardial infarction failing heart rats. J Mol Cell Cardiol. 2007;43(3):344-53. doi: 10.1016/j.yjmcc.2007.06.010.
100. Yoshida T, Watanabe M, Engelman DT, Engelman RM, Schley JA, Maulik N, et al. Transgenic mice overexpressing glutathione peroxidase are resistant to myocardial ischemia reperfusion injury. J Mol Cell Cardiol. 1996;28(8):1759-67. doi: 10.1006/jmcc.1996.0165.
101. Schupp N, Schmid U, Heidland A, Stopper H. Rosuvastatin protects against oxidative stress and DNA damage in vitro via upregulation of glutathione synthesis. Atherosclerosis. 2008;199(2):278-87. doi: 10.1016/j.atherosclerosis.2007.11.016.
102. Chen X, Guo C, Kong J. Oxidative stress in neurodegenerative diseases. Neural Regen Res. 2012;7(5):376-85. doi: 10.3969/j.issn.1673-5374.2012.05.009.
103. Behl T, Makkar R, Sehgal A, Singh S, Sharma N, Zengin G, et al. Current trends in neurodegeneration: cross talks between oxidative stress, cell death, and inflammation. doi: 10.3390/ijms22147432.
104. Yun HY, Dawson VL, Dawson TM. Neurobiology of nitric oxide. Crit Rev Neurobiol. 1996;10(3-4):291-316. doi: 10.1615/critrevneurobiol.v10.i3-4.20.
105. Aranda-Rivera AK, Cruz-Gregorio A, Arancibia-Hernandez YL, Hernandez-Cruz EY, Pedraza-Chaverri JP. Neurons and oxidative stress: An overview of basic concepts. Oxygen. 2022;2:437-78. doi: 10.3390/oxygen2040030.
106. Kokoszka JE, Coskun P, Esposito LA, Wallace DC. Increased mitochondrial oxidative stress in the SOD2 (+/-) mouse results in the age-related decline of mitochondrial function culminating in increased apoptosis. Proc Natl Acad Sci USA. 2001;98(5):2278-83. doi: 10.1073/pnas.051627098.
107. Wojda U, Salinska E, Kuznicki J. Calcium ions in neuronal degeneration. Life. 2008;60(9):575-90. doi: 10.1002/iub.91.
108. Emerit J, Edeas M, Bricaire F. Neurodegenerative diseases and oxidative stress. Biomed Pharmacol. 2004;58(1):39-46. doi: 10.1016/j.biopha.2003.11.004.
109. Mayer B, Oberbauer R. Mitochondrial regulation of apoptosis. Physiology. 2003;18(3):89-94. doi: 10.1152/nips.01433.2002.
110. Friedlander RM. Apoptosis and caspases in neurodegenerative diseases. New Engl J Med. 2003;348(14):1365-75. doi: 10.1056/NEJMra022366.
111. Niu Y, DesMarais TL, Tong Z, Yao Y, Costa M. Oxidative stress alters global histone modification and DNA methylation. Free Rad Biol Med. 2015;82:22-8. doi: 10.1016/j.freeradbiomed.2015.01.028.
112. Blaise GA, Gauvin D, Gangal M, Authier. Nitric oxide, cell signaling and cell death. Toxicology. 2005;208(2):177-92. doi: 10.1016/j.tox.2004.11.032.
113. Radi R. Nitric oxide, oxidants, and protein tyrosine nitration. Proc Natl Acad Sci USA. 2004;101(12):4003-8. doi: 10.1073/pnas.0307446101.
114. Lipton SA, Rosenberg PA. Excitatory amino acids as a final common pathway for neurologic disorders. New Engl J Med. 1994;330(9):613-22. doi: 10.1056/NEJM199403033300907.
115. Rosenberg RN. The molecular and genetic basis of Alzheimer's disease: the end of the beginning: the 2000 Wartenberg lecture. Neurology. 2000;54(11):2045-54. doi: 10.1212/wnl.54.11.2045.

CONTENT

116. Breijyeh Z, Karaman R. Comprehensive review on Alzheimer's disease: Causes and treatment. Molecules. 2020;25(24):5789. doi: 10.3390/molecules25245789.
117. Cheignon C, Tomas M, Bonnefont-Rousselot D, Faller P, Hureau C, Collin F, et al. Oxidative stress and the amyloid beta peptide in Alzheimer's disease. Redox Biol. 2018;14:450-64. doi: 10.1016/j.redox.2017.10.014.
118. Huang WJ, Zhang X, Chen WW. Role of oxidative stress in Alzheimer's disease. Biomed Rep. 2016;4(5):519-22. doi: 10.3892/br.2016.630.
119. Wang W, Zhao F, Ma X, Perry G, Zhu X. Mitochondria dysfunction in the pathogenesis of Alzheimer's disease: recent advances. Mol Neurodegen. 2020;15(30):1-22. doi: 10.1186/s13024-020-00376-6.
120. Koskenkorva-Frank TS, Weiss G, Koppenol WH, Burckhardt S. The complex interplay of iron metabolism, reactive oxygen species, and reactive nitrogen species: Insights into the potential of various iron therapies to induce oxidative and nitrosative stress. Free Rad Biol Med. 2013;65:1174-94. doi: 10.1016/j.freeradbiomed.2013.09.001.
121. Zhao Z. Iron and oxidizing species in oxidative stress and Alzheimer's disease. Aging Med. 2019;2(2):82-7. doi: /10.1002/agm2.12074.
122. Belaidi AA, Bush AI. Iron neurochemistry in Alzheimer's disease and Parkinson's disease: Targets for therapeutics. J Neurochem. 2016;139 Suppl 1:179197. doi: 10.1111/jnc.13425.
123. Hirschhorn T, Stockwell BR. The development of the concept of ferroptosis. Free Rad Biol Med. 2019;133:130-43. doi: 10.1016/j.freeradbiomed.2018.09.043.
124. Barnham KJ, McKinstry WJ, Multhaup G, Galatis D, Morton CJ, Curtain CC, et al. Structure of the Alzheimer's disease amyloid precursor protein copper binding domain. A regulator of neuronal copper homeostasis. J Biol Chem. 2003;278(19):17401-7. doi: 10.1074/jbc.M300629200.
125. Ejaz HW, Wang W, Lang M. Copper toxicity links to pathogenesis of Alzheimer's disease and therapeutics approaches. Int J Mol Sci. 2020;21(20):7660. doi: 10.3390/ijms21207660.
126. Christen Y. Oxidative stress and Alzheimer disease. Am J Clin Nut. 2000;71(2):S621-S629. doi: 10.1093/ajcn/71.2.621s.
127. Castegna A, Aksenov M, Aksenova M, Thongboonkerd V, Klein JB, Pierce WM, et al. Proteomic identification of oxidatively modified proteins in Alzheimer's disease brain. Part 1: creatine kinase BB, glutamine synthase, and ubiquitin carboxy-terminal hydrolase L-1. Free Rad Biol Med. 2002;33(4):562-71. doi: 10.1016/s0891-5849(02)00914-0.
128. Markesbery WR, Carney JM. Oxidative alterations in Alzheimer's disease. Brain Pathol. 2006;9(1):133-46. doi: 10.1111/j.1750-3639.1999.tb00215.x.
129. Liu Z, Li T, Li P, Wei N, Zhao Z, Liang H, et al. The ambiguous relationship of oxidative stress, Tau hyperphosphorylation, and autophagy dysfunction in Alzheimer's disease. Oxid Med Cell Longev. 2015;2015: 1-12. doi: 10.1155/2015/352723.
130. Blagov A, Borisov E, Grechko A, Popov M, Sukhorukov V, Orekhov A. The role of impaired mitochondrial transport in the development of neurodegenerative diseases. J Integr Neurosci. 2023;22(4):86. doi: 10.31083/j.jin2204086.
131. Cecerska-Heryć E, Polikowska A, Serwin N, Roszak M, Grygorcewicz B, Heryć R, et al. Importance of oxidative stress in the pathogenesis, diagnosis, and monitoring of patients with neuropsychiatric disorders, a review. Neurochem Int. 2022;153:105269. doi: 10.1016/j.neuint.2021.105269.
132. Hollen C, Neilson LE, Barajas RF Jr, Greenhouse I, Spain RI. Oxidative stress in multiple sclerosis-Emerging imaging techniques. Front Neurol. 2023;13:1025659. doi: 10.3389/fneur.2022.1025659.
133. 133. Chaudhary MR, Chaudhary S, Sharma Y, Singh TA, Mishra AK, Sharma S, et al. Aging, oxidative stress and degenerative diseases: mechanisms, complications and emerging therapeutic strategies. Biogerontology. 2023;24(5):609-62. doi: 10.1007/s10522-023-10050-1.
134. Alvarado JC, Fuentes-Santamaría V, Juiz JM. Frailty syndrome and oxidative stress as possible links between age-related hearing loss and Alzheimer's disease. Front Neurosci. 2022;15:816300. doi: 10.3389/fnins.2021.816300.
135. Saha S, Buttari B, Profumo E, Tucci P, Saso L. A perspective on Nrf2 signaling pathway for neuroinflammation: A potential therapeutic target in Alzheimer's and Parkinson's diseases. Front Cell Neurosci. 2022;15:787258. doi: 10.3389/fncel.2021.787258.
136. Boas SM, Joyce KL, Cowell RM. The NRF2-dependent transcriptional regulation of antioxidant defense pathways: Relevance for cell type-specific vulnerability to neurodegeneration and therapeutic intervention. Antioxidants (Basel). 2021;11(1):8. doi: 10.3390/antiox11010008.
137. Bai X, Bian Z, Zhang M. Targeting the Nrf2 signaling pathway using phytochemical ingredients: A novel therapeutic road map to combat neurodegenerative diseases. Phytomedicine. 2023;109:154582. doi: 10.1016/j.phymed.2022.154582.
138. Bhatia V, Sharma S. Role of mitochondrial dysfunction, oxidative stress and autophagy in progression of Alzheimer's disease. J Neurol Sci. 2021;421:117253. doi: 10.1016/j.jns.2020.117253.
139. Hyun DH, Lee J. A new insight into an alternative therapeutic approach to restore redox homeostasis and functional mitochondria in neurodegenerative diseases. Antioxidants (Basel). 2021;11(1):7. doi: 10.3390/antiox11010007.
140. Eren F, Yilmaz SE. Neuroprotective approach in acute ischemic stroke: A systematic review of clinical and experimental studies. Brain Circ. 2022;8(4):172-9. doi: 10.4103/bc.bc_52_22.
141. Li Z, Liu Y, Wei R, Yong VW, Xue M. The important role of zinc in neurological diseases. Biomolecules. 2022;13(1):28. doi: 10.3390/biom13010028.
142. Angeloni C, Malaguti M, Prata C, Freschi M, Barbalace MC, Hrelia S. Mechanisms underlying neurodegenerative disorders and potential neuroprotective activity of agrifood by-products. Antioxidants (Basel). 2022;12(1):94. doi: 10.3390/antiox12010094.
143. Esmaeili Y, Yarjanli Z, Pakniya F, Bidram E, Los MJ, Eshraghi M, et al. Targeting autophagy, oxidative stress, and ER stress for neurodegenerative disease treatment. J Cont Release. 2022;345:147-75. doi: 10.1016/j.jconrel.2022.03.001.
144. Uttara B, Singh AV, Zamboni P, Mahajan RT. Oxidative stress and neurodegenerative diseases: A review of

CONTENT

upstream and downstream antioxidant therapeutic options. Curr Neuropharmacol. 2009;7(1):65-74. doi: 10.2174/157015909787602823.
145. Spagnuolo C, Moccia S, Russo GL. Anti-inflammatory effects of flavonoids in neurodegenerative disorders. Europ J Med Chem. 2018;153:105-15. doi: 10.1016/j.ejmech.2017.09.001.
146. Dinkova-Kostova AT, Kostov RV, Kazantsev AG. The role of Nrf2 signaling in counteracting neurodegenerative diseases. FEBS J. 2018;285(19):35763590. doi: 10.1111/febs.14379.
147. Azam S, Haque ME, Jakaria M, Jo SH, Kim IS, Choi DK. G-protein-coupled receptors in CNS: A potential therapeutic target for intervention in neurodegenerative disorders and associated cognitive deficits. Cells. 2020;9(2):506. doi: 10.3390/cells9020506.
148. Lutjens R, Rocher JP. Recent advances in drug discovery of GPCR allosteric modulators for neurodegenerative disorders. Curr Opin Pharmacol. 2017;32:91-5. doi: 10.1016/j.coph.2017.01.001.
149. Hamilton A, Esseltine JL, DeVries RA, Cregan SP, Ferguson SSG. Metabotropic glutamate receptor 5 knockout reduces cognitive impairment and pathogenesis in a mouse model of Alzheimer's disease. Mol Brain. 2014;7:40. doi: 10.1186/1756-6606-7-40.
150. Yun HM, Rhim H. The serotonin-6 receptor as a novel therapeutic target. Exp Neurobiol. 2011;20(4):159-68. doi: 10.5607/en.2011.20.4.159.
151. Nirogi R, Jayarajan P, Shinde A, Mohammed AR, Grandhi VR, Benade V, et al. Progress in investigational agents targeting serotonin-6 receptors for the treatment of brain disorders. Biomolecules. 2023;13(2):309. doi: 10.3390/biom13020309.
152. Nunez MT, Chana-Cuevas P. New perspectives in iron chelation therapy for the treatment of neurodegenerative diseases. Pharmaceuticals. 2018;11(4):109. doi: 10.3390/ph11040109.
153. Verma S, Kumar A, Tripathi T, Kumar A. Muscarinic and nicotinic acetylcholine receptor agonists: current scenario in Alzheimer's disease therapy. J Pharm Pharmacol. 2018;70(8):985-93. doi: 10.1111/jphp.12919.
154. Leon R, Garcia AG, Marco-Contelles J. Recent advances in the multitarget-directed ligands approach for the treatment of Alzheimer's disease. Med Res Rev. 2013;33(1):139-89. doi: 10.1002/med.20248.
155. Sevigny J, Chiao P, Bussiere T, Weinreb PH, Williams L, Maier M, et al. The antibody aducanumab reduces Aβ plaques in Alzheimer's disease. Nature. 2016;537(7618):50-6. doi: 10.1038/nature19323.
156. Ferrero J, Williams L, Stella H, Leitermann K, Mikulskis A, O'Gorman J, et al. Firstin-human, double-blind, placebo-controlled, single-dose escalation study of aducanumab (BIIB037) in mild-to-moderate Alzheimer's disease. Alzheimer's & dementia: Transl Res Clin Interven. 2016;2(3):169-76. doi: 10.1016/j.trci.2016.06.002.
157. Shuai Q, He L, Wang Q, Wong YC, Mak M, Ho CY. Intranasal delivery of a novel acetylcholinesterase inhibitor HLS-3 for treatment of Alzheimer's disease. Life Sci 2018;207:428-35. doi: 10.1016/j.lfs.2018.06.032.
158. Patocka J, Jun D, Kuca K. Possible role of hydroxylated metabolites of tacrine in drug toxicity and therapy of Alzheimer's disease. Curr Drug Metabol. 2008;9(4):332-5. doi: 10.2174/138920008784220619.
159. Bolognesi ML, Bartolini M, Mancini F, Chiriano G, Ceccarini L, Rosini M, et al. Bis (7)-tacrine derivatives as multitarget-directed ligands: Focus on anticholinesterase and antiamyloid activities. Chem Med Chem 2010;5(8):1215-20. doi: 10.1002/cmdc.201000086.
160. World Health Organization. [Internet]. Cancer Factsheet. 2022. [Cited: 10-Jan-2024]. Available at: https://www.who.int/news-room/fact-sheets/detail/cancer
161. Mattiuzzi C, Lippi G. Current cancer epidemiology. J Epidemiol Glob Health. 2019;9(4):217-22. doi: 10.2991/jegh.k.191008.001.
162. Harris IS, DeNicola GM. The complex interplay between antioxidants and ROS in cancer. Trends Cell Biol. 2020;30(6):440-51. doi: 10.1016/j.tcb.2020.03.002.
163. Walton EL. The dual role of ROS, antioxidants and autophagy in cancer. Biomed J. 2016; 39(2):89-92. doi: 10.1016/j.bj.2016.05.001.
164. Chio IC, Tuveson DA. ROS in cancer: The burning question. Trend Mol Med. 2017;23(5):411-29. doi: 10.1016/j.molmed.2017.03.004.
165. Sabharwal SS, Schumacker PT. Mitochondrial ROS in cancer: Initiators, amplifiers or an Achilles' heel? Nature Rev Cancer. 2014;14:709-21. doi: 10.1038/nrc3803.
166. WhiteE. Autophagy and p53. Cold Spring Harb Perspect Med. 2016;6(4):a026120. doi: 10.1101/cshperspect.a026120.
167. Li Z, Yang Y, Ming M, Liu B. Mitochondrial ROS generation for regulation of autophagic pathways in cancer. Biochem Biophys Res Commun. 2011;414(1):5-8. doi: 10.1016/j.bbrc.2011.09.046.
168. Tal MC, Sasai M, Lee HK, Yordy B, Shadel GS, Iwasaki A. Absence of autophagy results in reactive oxygen species-dependent amplification of RLR signaling. Proc Natl Acad Sci USA. 2009;106(8):2770-5. doi: 10.1073/pnas.0807694106.
169. Li L, Ishdorj G, Gibson SB. Reactive oxygen species regulation of autophagy in cancer: Implications for cancer treatment. Free Rad Biol Med. 2012;53(7):1399-410. doi: 10.1016/j.freeradbiomed.2012.07.011.
170. Reczek CR, Chandel NS. ROS-dependent signal transduction. Curr Opinion Cell Biol. 2015;33:8-13. doi: 10.1016/j.ceb.2014.09.010.
171. Lee SR, Yang KS, Kwon J, Lee C, Jeong W, Rhee SG. Reversible inactivation of the tumor suppressor PTEN by H2O2. J Biol Chem. 2002;277(23):20336-42. doi: 10.1074/jbc.M111899200.
172. Salmeen A, Andersen JN, Myers MP, Meng TC, Hinks JA, Tonks NK, et al. Redox regulation of protein tyrosine phosphatase 1B involves a sulphenyl-amide intermediate. Nature. 2003;423:769-73. doi: 10.1038/nature01680.
173. Son Y, Cheong YK, Kim NH, Chung HT, Kang DG, Pae HO, et al. Mitogen-activated protein kinases and reactive oxygen species: How can ROS activate MAPK pathways? J Signal Trans. 211;792639. doi: 10.1155/2011/792639.
174. Hurd TR, DeGennaro, Lehmann R. Redox regulation of cell migration and adhesion. Trends Cell Biol. 2012;22(2):107-15. doi: 10.1016/j.tcb.2011.11.002.
175. Barrett CW, Ning W, Chen X, Smith JJ, Washington MK, Hill KE, et al. Tumor suppressor function of the plasma glutathione peroxidase Gpx3 in colitis-associated carcinoma. Cancer Res. 2013;73(3):1245-55. doi: 10.1158/0008-5472.CAN-12-3150.

CONTENT

176. Porporato PE, Payen VL, Perez-Escuredo J, Saedeleer CJD, Danhier P, Copetti T, et al. A mitochondrial switch promotes tumor metastasis. Cell Rep. 2014;8(3):754-66. doi: 10.1016/j.celrep.2014.06.043.
177. Melo D, Ribeiro S, Santos-Silva A, Rocha S. Rol of peroxiredoxin 2 in erythrocyte antioxidant defense: Peroxidase and chaperone. Free Rad Biol Med. 2018;120:S83. doi: 10.1016/j.freeradbiomed.2018.04.274.
178. Lippman SM, Klein EA, Goodman PJ, Lucia MS, Thompson IM, Ford LG, et al. Effect of selenium and vitamin E on risk of prostate cancer and other cancers: The selenium and vitamin E cancer prevention trial (SELECT). JAMA. 2009;301(1):39-51. doi: 10.1001/jama.2008.864.
179. 179. Gal KL, Ibrahim MX, Wiel C, Sayin VI, Akula MK, Karlsson C, et al. Antioxidants can increase melanoma metastasis in mice. Sci Transl Med. 2015;7(308):308re8. doi: 10.1126/scitranslmed.aad3740.
180. Jaune-Pons E, Vasseur S. Role of amino acids in regulation of ROS balance in cancer. Arch Biochem Biophy. 2020;689:108438. doi: 10.1016/j.abb.2020.108438.
181. Son J, Lyssiotis CA, Ying H, Wang X, Hua S, Ligorio M, et al. Glutamine supports pancreatic cancer growth through a KRAS-regulated metabolic pathway. Nature. 2013;496:101-5. doi: 10.1038/nature12040.
182. Piskounova E, Agathocleous M, Murphy MM, Hu Z, Huddlestun SE, Zhao Z, et al. Oxidative stress inhibits distant metastasis by human melanoma cells. Nature. 2015;527(7577):186-91. doi: 10.1038/nature15726.
183. Ogrunc M, Micco RD, Liontos M, Bombardelli L, Mione M, Fumagalli M, et al. Oncogene-induced reactive oxygen species fuel hyperproliferation and DNA damage response activation. Cell Death Differ. 2014;21:998-1012. doi: 10.1038/cdd.2014.16.
184. Budanov AV. The role of tumor suppressor p53 in the antioxidant defense and metabolism. Subcell Biochem. 2014;85:337-58. doi: 10.1007/978-94-017-9211-0_18.
185. Cao L, Xu X, Cao LL, Wang RH, Coumoul X, Kim SS, et al. Absence of full-length Brca1 sensitizes mice to oxidative stress and carcinogen-induced tumorigenesis in the esophagus and forestomach. Carcinogenesis 2007;28(7):1401-7. doi: 10.1093/carcin/bgm060.
186. Pucci C, Martinelli C, Ciofani G. Innovative approaches for cancer treatment: Current perspectives and new challenges. Ecancermedicalscience. 2019;13:961. doi: 10.3332/ecancer.2019.961.
187. Singh B, Sharma B, Kanwar SS, Kumar A. Lead phytochemicals for anticancer drug development. Front Plant Sci. 2016;7:1667. doi: 10.3389/fpls.2016.01667.
188. Perillo B, Donato MD, Pezone A, Zazzo ED, Giovannelli P, Galasso G, et al. ROS in cancer therapy: The bright side of the moon. Exp Mol Med. 2020;52(2):192-203. doi: 10.1038/s12276-020-0384-2.
189. Magda D, Miller RA. Motexafin gadolinium: A novel redox active drug for cancer therapy. Sem Cancer Biol. 2006;16(6):466-76. doi: 10.1016/j.semcancer.2006.09.002.
190. Tacar O, Sriamornsak P, Dass CR. Doxorubicin: An update on anticancer molecular action, toxicity and novel drug delivery systems. J Pharm Pharmacol. 2013;65(2):157-70. doi: 10.1111/j.2042-7158.2012.01567.x.
191. Griffith OW, Meister A. Potent and specific inhibition of glutathione synthesis by buthionine sulfoximine (S-n-butyl homocysteine sulfoximine). J Biol Chem. 1979 Aug 25;254(16):7558-60. PMID: 38242.
192. Moulder S, Dhillon N, Ng C, Hong D, Wheler J, Naing A, et al. A phase I trial of imexon, a pro-oxidant, in combination with docetaxel for the treatment of patients with advanced breast, non-small cell lung and prostate cancer. Invest New Drugs. 2010;28(5):634-40. doi: 10.1007/s10637-009-9273-1.
193. Kim SJ, Kim HS, Seo YR. Understanding of ROS-inducing strategy in anticancer therapy. Oxid Med Cell Longev. 2019;5381692-12. doi: 10.1155/2019/5381692.
194. Bersuker K, Hendricks JM, Li Z, Magtanong L, Ford B, Tang PH, et al. The CoQ oxidoreductase FSP1 acts parallel to GPX4 to inhibit ferroptosis. Nature. 2019;575:688-92. doi: 10.1038/s41586-019-1705-2.
195. Doll S, Freitas FP, Shah R, Aldrovandi M, Silva MC, Ingold I, et al. FSP1 is a glutathione-independent ferroptosis suppressor. Nature. 2019;575:693-8. doi: 10.1038/s41586-019-1707-0.
196. Martinelli C, Pucci C, Ciofani G. Nanostructured carriers as innovative cancer diagnosis and therapy tools. APL Bioengineering. 2019;3(1):011502. doi: 10.1063/1.5079943.
197. Bazak R, Houri M, Achy SE, Kamel S, Refaat T. Cancer active targeting by nanoparticles: a comprehensive review of literature. J Cancer Res Clinical Oncol. 2015;141(5):769-84. doi: 10.1007/s00432-014-1767-3.
198. Lebedeva IV, Su ZZ, Sarkar D, Fisher PB. Restoring apoptosis as a strategy for cancer gene therapy: Focus on p53 and Mda-7. Sem Cancer Biol. 2003;13(2):169-78. doi: 10.1016/s1044-579x(02)00134-7.
199. Brace C. Thermal tumor ablation in clinical use. IEEE Pulse. 2011;2(5):28-38. doi: 10.1109/MPUL.2011.942603.
200. Chikara S, Nagaprashantha LD, Singhal J, Horne D, Awasthi S, Singhal SS. Oxidative stress and dietary phytochemicals: Role in cancer chemoprevention and treatment. Cancer Lett. 2018;413:122-34. doi: 10.1016/j.canlet.2017.11.002.

CONTENT

Wahyuni et al. Scr Med. 2024 Mar-Apr;55(2):219-29. DOI:10.5937/scriptamed55-47959
REVIEW ARTICLE

Discovering the Impact of Bullying on Adolescents Through Bibliometric Analysis

Sri Wahyuni,[1] Satriya Pranata,[2] Wawan Kurniawan,[1] Rahayu Setyowati,[1] Heni Heni,[1] Arni Wianti,[1] Aat Agustini,[1] Hera Hijriani[1]

Abstract

In recent years, the number of bullying cases, especially among teenagers, has been increasing, with many mass media reports on bullying cases that have resulted in the death of the victim. The aim of the study was to explore the impact of bullying on adolescents by analysing of network visualisation, overlay visualisation and density visualisation on the topic through bibliometric analysis. Records were identified through a database search at *https://app.dimensions.ai/*. The data obtained was then selected further by the preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram. Papers were limited to publication years 2019-2023 and focussed on the fields of psychology, human society, health science, clinical biomedicine, clinical education and health psychology. Data were analysed using *VOSviewer*, then reviewed by co-occurrence and co-author. After identifying the clusters, the impacts of bullying on adolescents were suicidal behaviour, mental disorders, non-suicidal self-injury (NSSI), loneliness, psychological distress and adolescent childhood experiences (ACEs). From the overlay visualisation, it was indicated that the newest topics that were being widely researched related to the impact of bullying on adolescents were social anxiety, suicidal ideation, depressive symptoms, suicidal thought, integrated behaviour change (IBC) and peer victimisation. From density visualisation, it was indicated that topics that were rarely researched related to the topic of the impact of bullying on adolescent were suicide attempts, early victimisation, post-traumatic stress disorder (PTSD) and suicidality. The theme regarding the impact of bullying needs and developed to be researched more deeply, especially on themes with low visualisation found in density visualisation, in order to enrich the variety of research.

Key words: Impact; Bullying; Adolescent; *VOSviewer*; Bibliometric analysis.

1. Department of Nursing, Faculty of Health Science, YPIB Majalengka University, West Java, Indonesia.
2. Department of Nursing, Faculty of nursing and Health Science, Universitas Muhammadiyah Semarang, Indonesia.

Citation:
Wahyuni S, Pranata S, Kurniawan W, Setyowati R, Heni H, Wianti A, et al. Discovering the impact of bullying on adolescents through bibliometric analysis. Scr Med. 2024 Mar-Apr;55(2):219-29.

Corresponding author:
SRI WAHYUNI
E: yuyunyuni363@gmail.com

Received: 29 November 2023
Revision received: 19 January 2024
Accepted: 19 January 2024

Introduction

Adolescence is a time full of dynamics, since at this time teenagers begin to experience various new things starting from romance, solidarity in friendship, trying something new and challenging, a period of searching for identity, exploring new and different worlds to find out who they are.[1] The character of adolescent who tend to be unstable and sensitive encourages teenagers to behave according to their wishes without thinking about the risks that might occur in the future. Adolescents also often follow trends and follow what their friends are doing. This is the part where teenagers try to assert themselves as individuals or as members of a particular social group.[2]

Copyright © 2024 Wahyuni et al. This is an open access article distributed under the Creative Commons Attribution License (CC BY), which permits unrestricted use, distribution and reproduction in any medium, provided the original work is properly cited.

CONTENT

The formation of youth groups in a larger community will lead to the existence of superior individuals or groups and *vice versa*.[3] Sometimes superior groups show their identity as a group or individually in bad ways, for example violence, both physical and verbal. Violence that is more often shown by teenagers, for example is acts of bullying. Bullying itself is a hostile act carried out by one person or a group of people with the aim of frightening or hurting other people and occurs repeatedly and there is an imbalance of power between the victim and the perpetrator. However, bullying itself is a cycle, in the sense that the current perpetrator is most likely the victim of a previous perpetrator of bullying.[4]

Generally, adolescents who have economic and physical disadvantages (disabilities) easily become victims of bullying by their friends.[5] There are various forms of bullying, it can take the form of teasing, insults or beatings. The latest is bullying *via* social media which is conveyed through the comments column or statuses posted by the perpetrators which contain harsh words and curses at someone.[6] Not infrequently there are comment wars containing negative comments. In the school environment, bullying is usually carried out by strong students and of course the victims are weak students, or students who consider themselves superior carry out bullying actions against students they consider inferior.[7]

Bullying behaviour can have a bad impact on victims, especially adolescents, for example reducing their enthusiasm for studying at school, school strikes, stress, low self-esteem, trauma, fear at school, suicide and can even make children imitate bullying behaviour.[8] The purpose of study was to explore the impact of bullying on adolescent by analysed of network visualisation, overlay visualisation and density visualisation on the topic through bibliometric analysis.

Methods

In this research, bibliometric analysis was used. Records were identified through database searches *https://app.dimensions.ai/*. *Dimensions* is a database of abstracts and citations and of research grants, which links grants to resulting publications, clinical trials and patents. *Dimensions* is part of *Digital Science & Research Solutions Ltd*, a technology company headquartered London, United Kingdom.[9] The data obtained was then selected further by the preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram.[10] Papers were limited to publication year 2019-2023, focussed on the fields of psychology, human society, health science, clinical biomedical, clinical education and health psychology. Article was the type of publication that was analysed. Data were analysed using *VOSviewer* then reviewed by co-occurrence and co-author. Data was collected on 3 November 2023.

Selecting data

Data selection was carried out using the stages in PRISMA including identification, filtering and inclusion as shown in Figure 1. Stage 1 (identification) detected 161,344 records from *https:app.dimensions.ai/*, taking into account, each of the main search terms (impact AND bullying AND adolescent), "article document type" and "all published data range from 2019 to 2023". In stage 2 (screening), the option "title, article, abstract" was selected in the field of each search term, resulting in 45,813 articles. In stage 3 (included), the final sample yielded 34,364 articles.

Data analysis

Data were analysed using *VOSviewer*. *VOSviewer* is a software tool for building and visualising bibliometric networks. These networks can include individual journals, researchers, or publications and all of these can be obtained by citation, bibli-

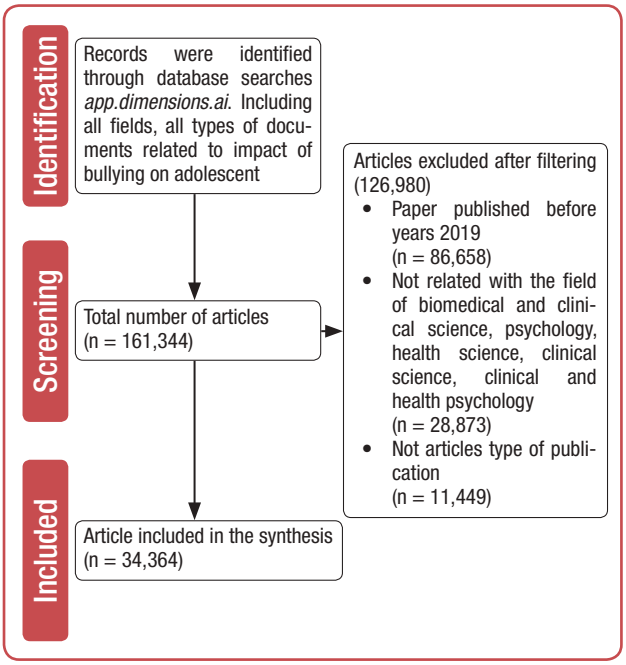


Figure 1: The preferred reporting items for systematic reviews and meta-analyses (PRISMA) flowchart

CONTENT

ographical merge, co-citation or co-author links. *VOSviewer* also offers text mining functionality which can be used to build and visualise co-occurrence networks of key terms extracted from collections of scientific literature.[11] The analysis type was selected to create maps based on text data. In this study, analyses were reviewed by co-occurrence and co-authors.

Co-occurrence procedures

The co-occurrence analysis procedure went through several steps, namely selecting the data source, reading data from the reference manager file. "Fields from which terms will be extracted" was selected, then "title and abstract fields" and "ignore structured abstract labels and ignore copyright statements" was chosen, then the "full counting" calculation method was selected. The minimum threshold for the appearance of a selected term was 10. Number of terms to be selected was 198.

Co-authors procedures

The co-authors analysis procedure went through the following stages: Selecting the type of data: "create a map based on bibliographic data". Next, select the data source "read data from references manager files". Select a file type that RIS supports. Select the analysis type and calculation method: "co-authorship analysis type and full calculation method". Select "choose type of analysis and calculating method". Click "co-authorship" as the type of analysis and click "full counting" as the counting method. Select "maximum number of authors" per document as 25. Of the 2169 authors, 9 met the threshold. An author for each of the 9 authors was selected. Total co-author links with other authors were counted. Authors with total spread links were selected. After verification, the number of authors was 9.

Results

Network visualisation of the impact of bullying on adolescents concept in publications

In Figure 2, it can be seen that there were 198 items divided into 9 clusters, 6,205 links, with a total link strength of 35,460. Two items connected by a line indicate that they appear together in the title and abstract of each study. After identifying the clusters, the impact of bullying on adolescent were suicidal behaviour, mental disorder, NSSI, loneliness, psychological distress and ACEs.

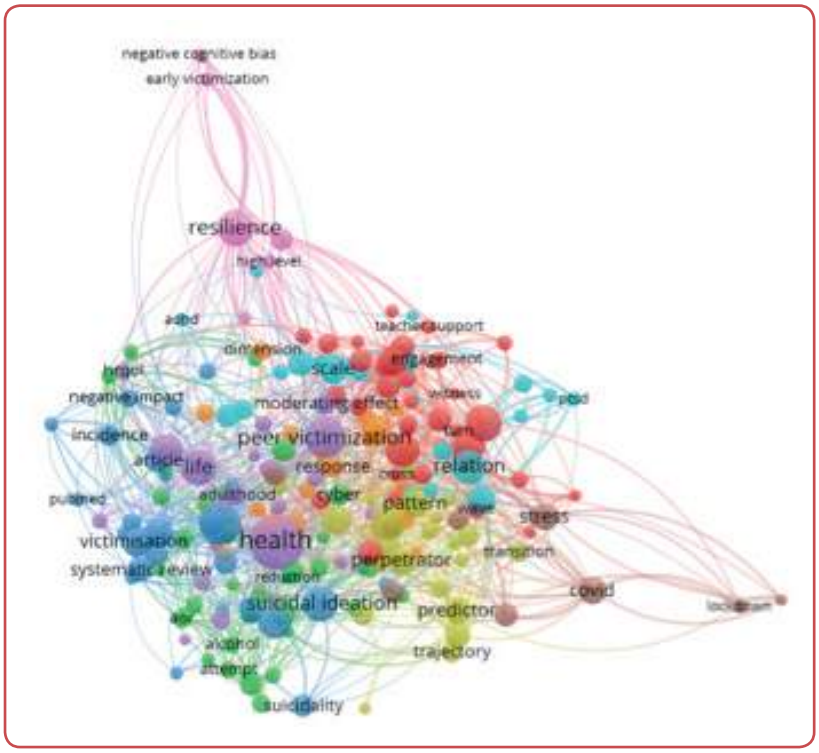


Figure 2: Network visualisation (source: VOSviewer)

CONTENT

Overlay visualisation of the anxiety among adolescents concept in publications

In Figure 3, the overlay visualisation, it can be indicated that research related to the impact of bullying on adolescents focusing on were social anxiety, suicidal ideation, depressive symptom, suicidal thought, integrated behaviour change (IBC) and peer victimisation.

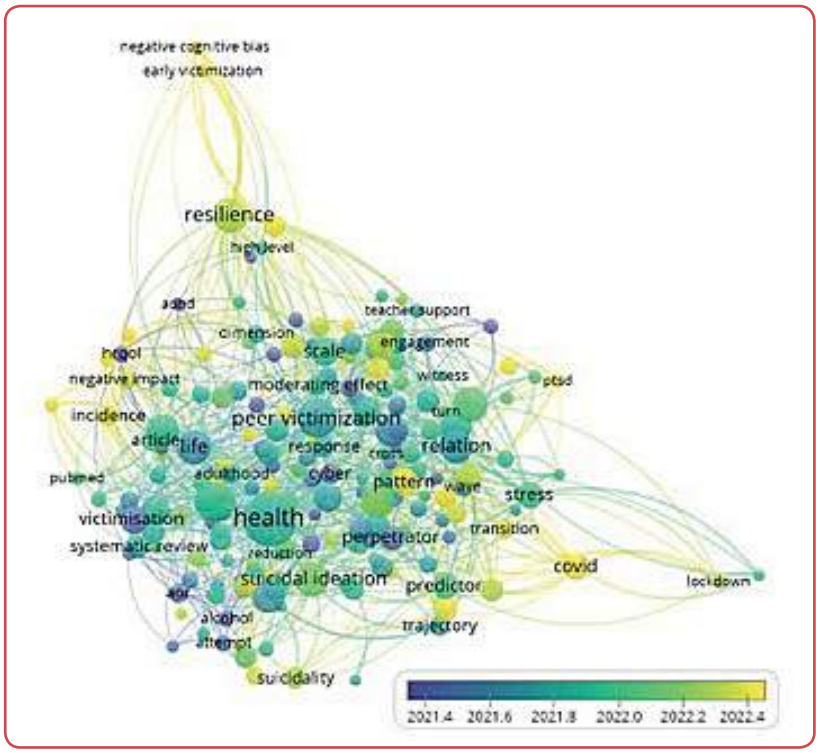


Figure 3: Overlay visualisation (source: VOSviewer)

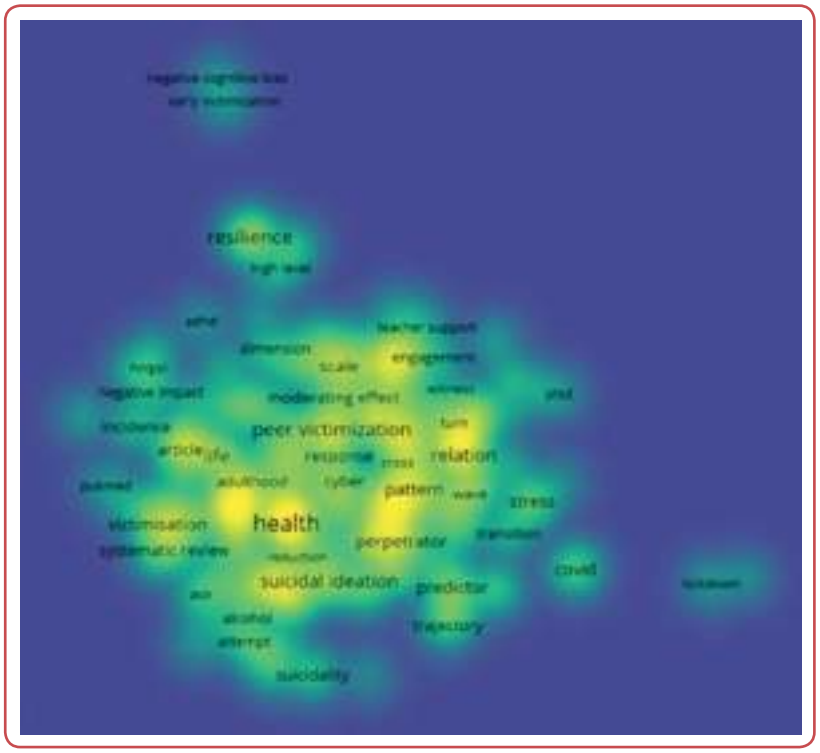


Figure 4: Density visualisation (source: VOSviewer)

CONTENT

Density visualisation of the anxiety among adolescents concept in publications

In Figure 4, from density visualisation it can be seen that topics with visualisation in the low category are suicide attempt, early victimisation, PTSD and suicidality.

Discussion

From the network visualisation, it was identified that there were 198 items divided into 9 clusters with a number of links 6,205 with a total link strength of 35,460. After identifying the clusters, the impact of bullying on adolescent were suicidal behaviour,[12] mental disorder,[13] NSSI,[14] loneliness,[15] psychological distress[16] and ACEs.[17]

From overlay visualisation, it was indicated that the newest topics that were widely researched related to the impact of bullying on adolescents were social anxiety,[18] suicidal ideation,[19] depressive symptoms,[20] suicidal thoughts,[21] integrated behaviour change (IBC)[22] and peer victimisation.[23] From density visualisation, it was indicated that topics that were rarely researched related to the topic of the impact of bullying on adolescents were suicide attempts,[24] early victimisation,[25] post-traumatic stress disorder (PTSD)[26] and suicidality.[27]

Suicidal behaviour, suicidal ideation and suicide attempt

The impact that occurs on victims of bullying can carry over into adulthood and is a serious problem that needs to be treated quickly. The emergence of depression in victims of bullying can lead to thoughts of suicide or self-harm because bullying that occurs to someone can make that person feel depressed.[28] Bullying has the impact of causing someone to experience depression if they do not receive immediate treatment and can give rise to other serious problems such as suicidal ideation or self-harm.[29]

Suicidal ideation is thoughts that lead to death, the individual plans to die by specifically eliminating life.[21] This statement illustrates that suicide leads to planned thoughts about taking one's life by committing suicide. There is a series of occurrences of suicidal behaviour, namely suicidal ideation, suicidal movements, suicidal attempts and suicide.[30] A person's idea of suicide will lead to thinking about what actions they can take to commit suicide before entering the stage of suicide. Suicide is the main cause of death in the world with the age range of suicide perpetrators being 15 to 29 years old.[28]

Mental disorder

According to the Centers for Disease Control and Prevention (CDC), bullying can have an impact on a person's physical and emotional health, both short and long term. Apart from that, victims of bullying can also experience physical injuries, social problems, emotional problems and even increase the risk of suicide and death. This is because victims of bullying become less self-confident and experience an increased risk of mental disorders.[31]

Apart from that, based on a study conducted by the Eunice Kennedy Shriver National Institute of Child Health and Human Development in the United States, anyone involved in bullying, whether victim or perpetrator, is at high risk of experiencing depression.[32] The risk of depression can even be higher in victims of electronic bullying, for example *via* social media, text messages or emails, compared to direct bullying. The Mayo Clinic in the United States also states the same, that victims of bullying can be at high risk of experiencing mental and other health disorders.[33]

Non-suicidal self-injury (NSSI)

Bullying is a real situation experienced by teenagers every day. Bullying can be done by classmates, even those closest to person. Bullying that occurs continuously without being handled properly can cause feelings of depression, lack of self-confidence and even traumatic feelings.[14] These feelings of pressure and lack of self-confidence can encourage victims of bullying to commit acts of NSSI as a form of desire to punish themselves and hate themselves.[34]

The results of research by Wilson et al[35] also found self-injury behaviour and suicidal thoughts in teenage victims of bullying. The tendency to carry out self-injury behaviour and suicidal intentions is based on the development of a sensitive brain during adolescence so that it has a higher vulnerability to trigger stress.[36]

Loneliness

Loneliness causes someone who experiences it

CONTENT

to feel empty, alone and unwanted even though the person is actually not alone and is in a busy environment.[15] This feeling of loneliness can occur in teenagers who experience bullying or are victims of bullying and teenagers who carry out bullying or are perpetrators of bullying. Teenagers who are victims of bullying usually feel isolated and ostracised by their group, friends and their social relationships are poor. As Sullivan said, people who have been intimidated often have difficulty forming good relationships, and tend to find it difficult to live a normal life.[30] Victims of bullying, according to a Royal College of Psychiatrists report, have low self-confidence, have few friends, spend time alone and often suffer from anxiety, difficulty sleeping, depression and suicide.[37]

Meanwhile, teenagers who become perpetrators of bullying usually do so because their behaviour is considered a threat, so their peers are shunned, avoided or even rejected in a group, causing them to feel lonely. Children who are bullies show negative characteristics such as being angry, depressed and are at risk of being involved in criminal behaviour as adults.[30] Bullies have low empathy for other people. Meanwhile, children who are victims of bullying based on research by Phan et al[38] are depressive, passive and shy.

Psychological distress

Adolescence is a time of searching for identity, they are faced with many new roles and status as adult humans. A positive self-identity will be formed if teenagers are able to explore new roles in a healthy way and find a positive path.[39] On the other hand, identity confusion arises because teenagers do not explore different roles and do not find positive paths, which can lead to delinquency such as bullying. Bullying is a secret action, while the victims (even eyewitnesses) do not dare to report it.[32]

Being a victim is a painful experience, holding onto events over and over again is difficult. The condition of the victims where every day they are harassed, hurt, humiliated repeatedly, leads to the feelings of insecurity, psychological shock, trauma and even mental disorders.[40]

Adolescent childhood experiences (ACEs)

Bullying behaviour generally does not just appear, but is influenced by several factors. Factors that influence bullying behaviour according to Soares et al[17] are: (a) personality factors, (b) family factors, (c) adverse childhood experience (ACE) factors, (d) school environmental factors. Children who live in unfavourable and dysfunctional family environments, the inability to resolve conflicts or in short, children who experience ACE are more at risk of becoming perpetrators of bullying because they reflect the naturalisation of violent behavioural practices or even interpreting aggressive behaviour towards peers as a joke.[41]

One of the factors that influences the emergence of bullying behaviour is ACE which is a term that refers to exposure to potentially traumatic events experienced by individuals during childhood aged 0-18 years.[42] Five characteristics of ACE: 1. Harmful (harmful) ACE – experiences that are harmful to children, 2. Chronic/recurring (chronic/appearing repeatedly times) ACE that are often repeated are a manifestation of chronic problems, 3. Distressing (causing suffering) ACE make children suffer or be depressed, 4. Cumulative (cumulative) ACE - children who experiencing more than one event or experiencing multiple traumatic events in a chronic and prolonged manner, and 5. Varying in severity (having varying degrees of severity) ACE characterised by varying degrees of severity from less to more severe.[43]

Social anxiety

A child who experiences bullying carried out by his friends at school or outside school will create feelings of self-doubt, insecurity and anxiety. This is supported by research that has been carried out. The results of these studies mostly explain that children who are victims of bullying will experience high levels of anxiety and this can have an impact on the child's self-esteem.[18] World Health Organization[30] states that mental health nurses are the largest health workforce in the entire world, namely 40 %, therefore it is hoped that nurses will be able to intervene to reduce anxiety in victims of bullying.

Anxiety is a very normal and frequently occurring human emotional response that involves aspects such as affective and cognitive behaviour to danger. This is seen as normal as part of childhood. Feelings of excessive and uncontrolled worry also include anxiety which is a response to internal and external stimuli which can cause emotional, cognitive, physical and behavioural symptoms.[44] The impact of anxiety

CONTENT

depends on the child's developmental level and the development of coping skills at that age. In school children, the effects that often occur are changes in sleep patterns, changes in eating patterns, anxiety, feelings of worthlessness, poor self-efficacy, difficulty concentrating, feelings of irritability, withdrawal, poor school performance, nightmares, aggressive behaviour, excessive worry and so on.[45]

Apart from that, the level of self-esteem can influence and cause social anxiety in children. Adolescence requires high self-esteem so that the child develops a sense of self-confidence, self-respect and looks strong.[46] If the need for self-esteem is not met, a feeling of inferiority, worthlessness and a feeling of helplessness and mental weakness will arise. Conditions that are usually experienced by children who are victims of bullying are that they appear withdrawn, quiet, restless and anxious.[47]

Depressive symptoms

Depression is defined as a mental disorder with signs and symptoms including feelings of depression, loss of interest and pleasure, decreased energy, feelings of guilt, anxiety and poor concentration.[48] Depression is a trigger for illness and disability in adolescents. One of the factors that makes teenagers vulnerable to depression is bullying. Identification of symptoms of depression in adolescents is important to study, especially as a result of bullying.[49]

In previous research in Indonesia, it was found that there was a positive relationship between experiencing bullying and depression in adolescents and bullying had an influence on the emergence of depression. These results were supported by other research which showed that the intensity of bullying behaviour experienced was directly proportional to the prevalence of depression. Adolescents who experience bullying behaviour with moderate intensity have a tendency to experience moderate depression of 66 %, while those who experience bullying behaviour with mild intensity have a tendency to experience mild depression of 33.3 %.[50]

Integrated behaviour change (IBC)

In this day and age where technology is so sophisticated that it is very easy for bullying to occur, simply usage of social media to bring down the victim by distributing negative photos or videos about the victim, causing the victim to experience mental health problems such as depression, anxiety, lack of self-confidence, difficulties to sleep, desire to hurt themself and even want to commit suicide.[51]

Some children who are often bullied at school usually have certain physical conditions, smart children, students who don't have friends and children who are economically disadvantaged. Bullying has long-term effects for both the victim and the perpetrator of the bullying themselves. The effect felt by victims is that they feel that their self-confidence has been taken away.[52]

Meanwhile, for the perpetrators of bullying, the effect will become a habit and enjoyment to increase their ego. The fear or trauma experienced by victims of bullying at school will trigger them to drop out of school, children who are victims of bullying at school will usually show changes in habits such as children often feeling afraid to go back to school, often experiencing nightmares, decreased appetite and changes in behaviour such as prefer to be alone, daydream, don't talk much and don't have self-confidence.[53] To overcome this bullying case, it is necessary to apply counselling theory, namely by using behavioural counselling theory.[54]

Peer and early victimisation

Bullying victimisation is a condition resulting from negative actions repeatedly and over time against negative actions by one or more other teenagers where in the bullying there is an imbalance of power or strength. The impacts that occur on victims of bullying include poor physical health,[2] disrupting mental health, such as depression and internalisation problems (anxiety, fear and withdrawal from the social environment)[55] as well as influencing individual psychosocial problems.[56] It is important to know the factors that can contribute to reducing bullying that occurs, especially from the victim's side. One potential protective factor is through quality friendships. The quality of friendship itself according to Yang et al[48] is a quality friendship relationship between a person and someone who is considered a good friend.

Gottman and Parker explained that support obtained from friendship can provide encouragement and feedback that can help teenagers to develop an impression of themselves as

CONTENT

competent, attractive and valuable figures. Then, with the support received, teenagers can get the physical help they need if they experience interference from other friends. Therefore, if teenagers have positive feelings towards themselves, such as feeling like they have high self-esteem are competent and attractive and get the necessary physical support, teenagers can avoid bullying victimisation that can occur.[57]

Friendship quality is an effective factor in preventing peer victimisation, such as high quality friendships.[58] Adolescents who have high levels of support from their friends have lower levels of bullying and victimisation.[15] Xiong et al[59] explained that individuals who have protective and reciprocal friendships can reduce children's involvement in bullying. Quality friendships can reduce individual involvement in bullying victimisation, because through best friends aggressive attacks from bullies can be avoided.[60] Zhang et al explains that the quality of friendship has five aspects, play/companionship (togetherness), conflict, help, security and closeness.[61]

Post-traumatic stress disorder (PTSD)

PTSD is a condition that some people experience after experiencing or witnessing a traumatic event. The hallmark of a traumatic event is its ability to induce feelings of fear, helplessness or horror in response to the threat of injury or death, so it can affect anyone, including victims of bullying.[48]

Research has shown that experiencing bullying is the strongest predictor of developing PTSD symptoms.[26] This number goes beyond physical abuse, neglect and exposure to community violence. Another literature review examining 29 relevant studies on bullying and harassment found that 57 % of victims scored above the threshold for meeting PTSD criteria.[62]

As teens approach adulthood, some PTSD symptoms in teens begin to look like those of adults. For example, they may have upsetting thoughts or memories, recurring nightmares, flashbacks and strong feelings of distress when reminded of the event. The difference is that teenagers are more likely to exhibit impulsive and aggressive behaviour than young children or adults. Moreover, although children may be haunted by thoughts of painful experiences, this does not mean they can be easily observed. In fact, children often suffer in silence.[63]

Implication and limitation

This bibliometric analysis literature review has several limitations. First, there is limited literature available regarding IBC, which is almost the same as discussing the psychological impact on adolescent victims of bullying. The literature on suicidal behaviour, suicidal ideation and suicide attempt is used as one discussion because the same literature discusses this and in most of the other literature there is a mismatch between the criteria, samples and problems with the theme in question.

Conclusion

Bullying is a problem that is currently trending, especially among adolescent, the impact of bullying both physically and psychologically can traumatise the victim and affect their mental health, the theme regarding the impact of bullying needs to be developed to be researched more deeply, especially on themes with low visualisation found in density visualisation in order to enrich the variety of research.

Ethics

This study was a secondary analysis based on the currently existing dataset from the *Dimensions* and did not directly involve with human participants or experimental animals. Therefore, the ethics approval was not required in this paper.

Acknowledgement

The researchers are grateful to Universitas YPIB Majalengka, West Java, Indonesia for their help of funding support and Universitas Muhammadiyah Semarang Central Java Indonesia for collaborative relationship in research.

Conflicts of interest

The authors declare that there is no conflict of interest.

CONTENT

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Data access

The data that support the findings of this study are available from the corresponding author upon reasonable individual request.

Author ORCID numbers

Sri Wahyuni (SW):
0000–0002–7450–9841
Satriya Pranata (SP):
0000–0002–2026–8931
Wawan Kurniawan (WK):
0000–0002–8125–2001
Rahayu Setyowati (RS):
0000–0003–3048–3501
Heni Heni (HH):
0009–0004–8065–5169
Arni Wianti (AW):
0009–0009–5944–8153
Aat Agustini (AA):
0009–0007–5835–8426
Hera Hijriani (HHi):
0009–0004–7851–5730

Author contributions

Conceptualisation: SW, SP
Methodology: SW, SP
Writing - original draft: SW, SP
Formal analysis: WW, RS
Investigation: WW, RS
Validation: WW, RS
Data curation: HH, AW
Resources: HH, AW
Visualisation: HH, AW
Writing – review and editing: AA, HHi, SW
Project administration: AA, HHi, SW
Supervision: SP
Funding acquisition: WK

References

1. Falla D, Romera EM, Ortega-Ruiz R. Aggression, moral disengagement and empathy. A longitudinal study within the interpersonal dynamics of bullying. Front Psychol. 2021;12:703468. doi:10.3389/fpsyg.2021.703468.
2. Carrera-Fernández MV, Almeida A, Cid-Fernández XM, González-Fernández A, Fernández-Simo JD. Troubling secondary victimization of bullying victims: the role of gender and ethnicity. J Interpers Violence. 2021;37(15-16):np13623-np13653. doi:10.1177/08862605211005151.
3. Waterman EA, Banyard VL, Edwards KM, Mauer VA. Youth perceptions of prevention norms and peer violence perpetration and victimization: A prospective analysis. Aggress Behav. 2022;48(4):402-17. doi:10.1002/ab.22024.
4. Ren P, Wang Y, Liang Y, Li S, Wang Q. Bidirectional relationship between bullying victimization and functions of aggression in adolescents: The mediating effect of teacher justice. J Adolesc. 2023;95(6):1245-57. doi:10.1002/jad.12198.
5. Malinowska-Cieślik M, Kleszczewska D, Dzielska A, Ścibor M, Mazur J. Similarities and differences between psychosocial determinants of bullying and cyberbullying perpetration among Polish adolescents. Int J Environ Res Public Health. 2023;20(2):1358. doi:10.3390/ijerph20021358.
6. Labuhn M, LaBore K, Ahmed T, Ahmed R. Trends and instigators among young adolescent suicide in the United States. Public Health. 2021;199:51-56. doi:10.1016/j.puhe.2021.08.004.
7. Qin KN, Gan X. Longitudinal relationships between school assets, traditional bullying, and internet gaming disorder: the role of self-control and intentional self-regulation among Chinese adolescents. Front Public Heal. 2023;11:1162022. doi:10.3389/fpubh.2023.1162022.
8. Sasson H, Tur-Sinai A, Dvir K, Harel-Fisch Y. The role of parents and peers in cyberbullying perpetration: comparison among Arab and Jewish and youth in Israel. Child Indic Res. 2022;16(2):717-37. doi:10.1007/s12187-022-09986-6.
9. Hong JS, Zhang S, Espelage DL, Allen-Meares P. Dimensions of parenting and children's bullying victimization: a look at the racial/ethnic and grade level differences. J Genet Psychol. 2023;184(4):287-301. doi:10.1080/00221325.2023.2169104.
10. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021 Mar 29;372:n71. doi: 10.1136/bmj.n71.
11. van Eck NJ, Waltman L. Software survey: VOSviewer, a computer program for bibliometric mapping. Scientometrics. 2010;84(2):523-38. doi:10.1007/s11192-009-0146-3.
12. Lucas-Molina B, Pérez-Albéniz A, Solbes-Canales I, Ortuño-Sierra J, Fonseca-Pedrero E. Bullying, cyberbullying and mental health: the role of student connectedness as a school protective factor. Psychosoc Interv. 2021;31(1):33-41. doi:10.5093/pi2022a1.

CONTENT

13. Reisert H, Pham D, Rapoport E, Adesman A. Associations between bullying and condition severity among youth with chronic health conditions. J Adolesc Heal. 2023;73(2):279-87. doi:10.1016/j.jadohealth.2023.03.004.
14. Wang YJ, Li X, Ng CH, Xu DW, Hu S, Yuan TF. Risk factors for non-suicidal self-injury (NSSI) in adolescents: A meta-analysis. eClinicalMedicine. 2022;46:101350. doi:10.1016/j.eclinm.2022.101350.
15. John A, Lee SC, Puchades A, Del Pozo-Baños M, Morgan K, Page N, et al. Self-harm, in-person bullying and cyberbullying in secondary school-aged children: A data linkage study in Wales. J Adolesc. 2022;95(1):97-114. doi:10.1002/jad.12102.
16. Yosep I, Hikmat R, Mardhiyah A, Hazmi H, Hernawaty T. Method of nursing interventions to reduce the incidence of bullying and its impact on students in school: a scoping review. Healthcare. 2022;10(10):1835. doi:10.3390/healthcare10101835.
17. Soares S, Santos AC, Fraga S. Adverse childhood experiences, bullying, inflammation and BMI in 10-year-old children: The biological embodiment. PLoS One. 2022;17(8):e0273329. doi:10.1371/journal.pone.0273329.
18. Hu X, Xiao B. The effect of emotional neglect on cyberbullying among rural chinese left-behind adolescents—mediating role of social anxiety. Children. 2023;10(6):1055. doi:10.3390/children10061055.
19. Estévez-García JF, Cañas E, Estévez E. Non-disclosure and suicidal ideation in adolescent victims of bullying: an analysis from the family and school context. Psychosoc Interv. 2023;32(3):191-201. doi:10.5093/pi2023a13.
20. Darabos K, Mazza MC, Somers J, Song A V, Hoyt MA. Peer victimization and relationships to approach and avoidance coping to health and health behaviors. Behav Med. 2021;49(1):15-28. doi:10.1080/08964289.2021.1946468.
21. Hong JS, Choi J, Burlaka V, Burlaka J, Marsack-Topolewski CN, Voisin DR. Bullying victimization and suicidal thoughts: emotional distress and neighborhood conditions. Arch Suicide Res. 2023 Apr 4:1-13. doi:10.1080/13811118.2023.2192755.
22. Fraga S, Soares S, Peres FS, Barros H. Household dysfunction is associated with bullying behavior in 10-year-old children: do socioeconomic circumstances matter? J Interpers Violence. 2021;37(15-16):np13877-np13901. doi:10.1177/08862605211006352.
23. Martín-Pérez Á de L, Gascón-Cánovas JJ. The impact of the magnitude of the group of bullies on health-related quality of life and academic performance among adolescents. Child Psychiatry Hum Dev. 2021;54(3):796-805. doi:10.1007/s10578-021-01290-8.
24. Humphries KD, Li L, Smith GA, Bridge JA, Zhu M. Suicide attempts in association with traditional and electronic bullying among heterosexual and sexual minority U.S. high school students. J Adolesc Heal. 2021;68(6):1211-4. doi:10.1016/j.jadohealth.2020.12.133.
25. Gabrielli S, Rizzi S, Carbone S, Piras EM. School interventions for bullying–cyberbullying prevention in adolescents: insights from the UPRIGHT and CREEP projects. Int J Environ Res Public Health. 2021;18(21):11697. doi:10.3390/ijerph182111697.
26. Li T, Chen B, Li Q, Wu X, Li Y, Zhen R. Association between bullying victimization and post-traumatic stress disorders among Chinese adolescents: a multiple mediation model. BMC Psychiatry. 2023;23(1):758. doi:10.1186/s12888-023-05212-x.
27. Islam I, Yunus FM, Kabir E, Khanam R. Evaluating risk and protective factors for suicidality and self-harm in Australian adolescents with traditional bullying and cyberbullying victimizations. Am J Heal Promot. 2021;36(1):73-83. doi:10.1177/08901171211034105.
28. Veloso-Besio C, Cuadra-Peralta A, Gallardo-Peralta L, Cuadra-Fernandez P, Quiroz PT, Troncoso NV. The prevalence of suicide attempt and suicidal ideation and its relationship with aggression and bullying in Chilean adolescents. Front Psychol. 2023;14:1133916. doi:10.3389/fpsyg.2023.1133916.
29. Nguyen TH, Shah G, Muzamil M, Ikhile O, Ayangunna E, Kaur R. Association of in-school and electronic bullying with suicidality and feelings of hopelessness among adolescents in the United States. Children. 2023;10(4):755. doi:10.3390/children10040755.
30. Chiu H, Vargo EJ. Bullying and other risk factors related to adolescent suicidal behaviours in the Philippines: a look into the 2011 GSHS Survey. BMC Psychiatry. 2022;22(1):445. doi:10.1186/s12888-022-04085-w.
31. Lai W, Li W, Guo L, Wang W, Xu K, Dou Q, et al. Association between bullying victimization, coping style, and mental health problems among Chinese adolescents. J Affect Disord. 2022;324:379-86. doi:10.1016/j.jad.2022.12.080.
32. Alfonzo LF, Singh A, Disney G, King T. The mental health impact of school bullying among young carers in Australia: a causal mediation analysis. Sci Rep. 2023;13(1):16788. doi:10.1038/s41598-023-43464-5.
33. Augustine L, Bjereld Y, Turner R. The role of disability in the relationship between mental health and bullying: a focused, systematic review of longitudinal studies. Child Psychiatry Hum Dev. 2022 Oct 23. doi:10.1007/s10578-022-01457-x.
34. Zhao K, Tong S, Hong L, Yang S, Yang W, Xu Y, et al. Childhood trauma, peer victimization, and non-suicidal self-injury among Chinese adolescents: a latent variable mediation analysis. BMC Psychiatry. 2023;23(1):436. doi:10.1186/s12888-023-04848-z.
35. Wilson E, Crudgington H, Morgan C, Hirsch C, Prina M, Gayer-Anderson C. The longitudinal course of childhood bullying victimization and associations with self-injurious thoughts and behaviors in children and young people: A systematic review of the literature. J Adolesc. 2022;95(1):5-33. doi:10.1002/jad.12097.
36. Armitage R. Bullying in children: impact on child health. BMJ Paediatr Open. 2021;5(1):e000939. doi:10.1136/bmjpo-2020-000939.
37. Zhang Y, Li Z, Tan Y, Zhang X, Zhao Q, Chen X. The influence of personality traits on school bullying: a moderated mediation model. Front Psychol. 2021;12:650070. doi:10.3389/fpsyg.2021.650070.
38. Phan TC, Chau B, Do HN, Vu TBT, Vu KL, Nguyen HD, et al. Determinants of mental health among youths and adolescents in the digital era: Roles of cyber and traditional bullying, violence, loneliness, and environment factors. Front Public Heal. 2022;10:971487. doi:10.3389/fpubh.2022.971487.
39. Nuñez-Fadda SM, Castro-Castañeda R, Vargas-Jiménez E, Musitu-Ochoa G, Callejas-Jerónimo JE. Impact of bullying—victimization and gender over psychological distress, suicidal ideation, and family function-

CONTENT

ing of Mexican adolescents. Children. 2022;9(5):747. doi:10.3390/children9050747.
40. Sabramani V, Idris IB, Ismail H, Nadarajaw T, Zakaria E, Kamaluddin MR. Bullying and its associated individual, peer, family and school factors: evidence from Malaysian national secondary school students. Int J Environ Res Public Health. 2021;18(13):7208. doi:10.3390/ijerph18137208.
41. Shattnawi KK, Al Ali N, Ma'abreh YM. Prevalence of adverse childhood experiences and their relationship with self-esteem among school-age children in Jordan. Child Psychiatry Hum Dev. 2024 Feb;55(1):60-70. doi: 10.1007/s10578-022-01378-9.
42. Gajos JM, Miller CR, Leban L, Cropsey KL. Adverse childhood experiences and adolescent mental health: Understanding the roles of gender and teenage risk and protective factors. J Affect Disord. 2022;314:303-8. doi:10.1016/j.jad.2022.07.047.
43. Zhen-Duan J, Colombo D, Cruz-Gonzalez MA, Hoyos M, Alvarez K. Adverse childhood experiences and alcohol use and misuse: testing the impact of traditional and expanded adverse childhood experiences among racially/ethnically diverse youth transitioning into adulthood. Psychol Trauma. 2023;15(S1):s55-s64. doi:10.1037/tra0001458.
44. Islam MI, Khanam R, Kabir E. Depression and anxiety have a larger impact on bullied girls than on boys to experience self-harm and suicidality: A mediation analysis. J Affect Disord. 2021;297:250-8. doi:10.1016/j.jad.2021.10.061.
45. Iannello NM, Caravita S, Papotti N, Gelati C, Camodeca M. Social anxiety and bullying victimization in children and early adolescents: the role of developmental period and immigrant status. J Youth Adolesc. 2024 Jan;53(1):130-41. doi: 10.1007/s10964-023-01865-9.
46. Hamstra C, Fitzgerald M. Longitudinal effects from childhood abuse to bullying perpetration in adolescence: the role of mental health and social problems. J Child Adolesc Trauma. 2022;15(3):869-81. doi:10.1007/s40653-021-00409-2.
47. Cao G, Wei X, Liu J, Li X. The association between childhood trauma and adolescent cyberbullying: chain mediating roles of emotional intelligence and online social anxiety. Front Psychiatry. 2023;14:1184382. doi:10.3389/fpsyt.2023.1184382.
48. Yang X, Zhen R, Liu Z, Wu X, Xu Y, Ma R, et al. Bullying victimization and comorbid patterns of PTSD and depressive symptoms in adolescents: random intercept latent transition analysis. J Youth Adolesc. 2023 Nov;52(11):2314-27. doi: 10.1007/s10964-023-01826-2.
49. Park J, Lee H, Choi B, Kim JH, Yoon J, Yi H, et al. Adolescent bullying victimization at secondary school and adult suicidality and depressive symptoms among 2152 lesbian, gay, and bisexual adults in South Korea. Asia Pac J Public Health. 2022 May;34(4):338-45. doi: 10.1177/10105395211073283.
50. Fine SL, Pinandari AW, Muzir SM, Agnesia L, Novitasari PI, Bass JK, et al. "If it's really excessive, it can enter your heart": A mixed methods investigation of bullying among early adolescents in Semarang, Indonesia. J Interpers Violence. 2023 Feb;38(3-4):4088-113. doi: 10.1177/08862605221111422.
51. Kim JH, Hahlweg K, Schulz W. Early childhood parenting and adolescent bullying behavior: Evidence from a randomized intervention at ten-year follow-up. Soc Sci Med. 2021;282:114114. doi:10.1016/j.socscimed.2021.114114.
52. Shah R, Dodd M, Allen E, Viner R, Bonell C. Is being a victim of bullying or cyberbullying in secondary school associated with subsequent risk-taking behavior in adolescence? A longitudinal study in secondary schools. J Adolesc. 2022;94(4):611-27. doi:10.1002/jad.12050.
53. Jattamart A, Kwangsawad A. What awareness variables are associated with motivation for changing risky behaviors to prevent recurring victims of cyberbullying? Heliyon. 2021;7(10):e08121. doi:10.1016/j.heliyon.2021.e08121.
54. Yosep I, Hikmat R, Mardhiyah A. school-based nursing interventions for preventing bullying and reducing its incidence on students: a scoping review. Int J Environ Res Public Health. 2023;20(2):1577. doi:10.3390/ijerph20021577.
55. Tang W, Chen M, Wang N, Deng R, Tang H, Xu W, et al. Bullying victimization and internalizing and externalizing problems in school-aged children: The mediating role of sleep disturbance and the moderating role of parental attachment. Child Abuse Negl. 2023;138:106064. doi:10.1016/j.chiabu.2023.106064.
56. Roza TH, Yano VAN, Roza SA, Santo JB, da Cunha JM. Bullying victimization and friendship as influences on sleep difficulty among Brazilian adolescents. J Genet Psychol. 2021;182(5):348-60. doi:10.1080/00221325.2021.1905597.
57. Hensums M, de Mooij B, Kuijper SC, Fekkes M, Overbeek G. What works for whom in school-based anti-bullying interventions? An individual participant data meta-analysis. Prev Sci. 2023 Nov;24(8):1435-46. doi: 10.1007/s11121-022-01387-z.
58. Çopur EÖ, Kubilay G. The effect of solution-focused approaches on adolescents' peer bullying skills: A quasi-experimental study. J Child Adolesc Psychiatr Nurs. 2021;35(1):45-51. doi:10.1111/jcap.12348.
59. Xiong Y, Wang Y, Wang Q, Zhang H, Yang L, Ren P. Bullying victimization and depressive symptoms in Chinese adolescents: the roles of belief in a just world and classroom-level victimization. Eur Child Adolesc Psychiatry. 2022;32(11):2151-62. doi:10.1007/s00787-022-02059-7.
60. Roca-Campos E, Duque E, Ríos O, Ramis-Salas M. The zero violence brave club: a successful intervention to prevent and address bullying in schools. Front Psychiatry. 2021;12:601424. doi:10.3389/fpsyt.2021.601424.
61. Zhang J, Lin G, Cai Q, Hu Q, Xu Y, Guo Z, et al. The role of family and peer factors in the development of early adolescent depressive symptoms: A latent class growth analysis. Front Psychiatry. 2022 Sep 15;13:914055. doi: 10.3389/fpsyt.2022.914055.
62. Al-Darmaki F, Sabbah H Al, Haroun D. Prevalence of bullying behaviors among students from a national university in the United Arab Emirates: a cross-sectional study. Front Psychol. 2022;13:768305. doi:10.3389/fpsyg.2022.768305.
63. Idsoe T, Vaillancourt T, Dyregrov A, Hagen KA, Ogden T, Nærde A. Bullying victimization and trauma. Front Psychiatry. 2021;11:480353. doi:10.3389/fpsyt.2020.480353.

CONTENT

Sharma et al. Scr Med. 2024 Mar-Apr;55(2):231-43. DOI:10.5937/scriptamed55-46960

CURRENT TOPIC

Advent of Artificial Intelligence in Orthognathic Surgery: Advancements and Challenges

Anju Sharma,[1] Ginpreet Kaur,[1] Hardeep Singh Tuli,[2] Raunak Singh Chhabra,[3] Rashmi Rana[4]

1. Shobhaben Pratapbhai Patel School of Pharmacy and Technology Management, SVKM's NMIMS, Vile Parle, Mumbai, India.
2. Department of Bio-Sciences and Technology, Maharishi Markandeshwar Engineering College, Maharishi Markandeshwar (Deemed to Be University), Mullana-Ambala, Ambala, India.
3. Tech Mahindra, Pune, India.
4. Department of Research, Sir Ganga Ram Hospital, Delhi, India.

Citation:
Sharma A, Kaur G, Tuli HS, Chhabra RS, Rana R. Advent of artificial intelligence in orthognathic surgery: advancements and challenges. Scr Med. 2024 Mar-Apr;55(2):231-43.

Corresponding author:
GINPREET KAUR
E: ginpreet.kaur@nmims.edu

Abstract

Orthognathic surgery is a procedure used to correct facial deformities and jaw bone misalignment. The use of technology, specifically virtual surgical planning (VSP), has become increasingly prevalent in preoperative planning for orthognathic surgery. High-resolution computed tomography (CT) imaging has enabled computer-aided modelling. Artificial intelligence (AI) implementation has transformed orthognathic surgery methodology. This article highlights the latest market trends and modern-day advancements in the field, including the conventional and surgery first approach for orthognathic surgery. The use of computer-aided surgical simulation (CASS) in VSP for orthognathic surgery was studied. The different software used for orthognathic surgical planning and the detailed protocol followed during the surgery, including the preoperative procedure were discussed along with utilisation of 3-dimension cone-beam computed tomography (3D CBCT) images for surgical planning. The implementation of VSP with CASS had significantly enhanced the accuracy and efficiency of orthognathic surgery for dentofacial deformity correction. The use of technology allowed improved preoperative planning, resulting in better outcomes for patients. The study of different software for orthognathic surgical planning and the protocol followed during surgery has provided valuable insight into the surgery. The continued advancement of technology in orthognathic surgery is promising for the field and for the patients.

Key words: Artificial intelligence; Machine learning; Deep learning; Surgery-first approach; Computer aided design and manufacturing; Surgical system and cone beam computed tomography; Computer aided surgical simulation.

Received: 4 October 2023
Revision received: 23 January 2024
Accepted: 23 January 2024

Introduction

This review highlights the implications of artificial intelligence (AI) techniques integrated with orthognathic surgery. Various software is available for virtual surgical planning and challenges and complications associated with orthognathic surgery.

"AI is a broad transdisciplinary field, it is a branch of science and engineering that deals with machine understanding and is typically referred to as intelligent behaviour, with the creation of artifacts".[1, 2] It is a discipline in computer science that aims to understand and create intelligent entities, which are often manifested as software programs.[3] The use of AI to complete activities that traditionally require human intelligence is transforming numerous industries.[3, 4] Their capacity to identify meaningful associations in data

Copyright © 2024 Sharma et al. This is an open access article distributed under the Creative Commons Attribution License (CC BY), which permits unrestricted use, distribution and reproduction in any medium, provided the original work is properly cited.

CONTENT

collection can be utilised across diverse clinical scenarios for purposes such as diagnosis, treatment planning and predicting outcomes.[1]

The concept of AI was initially introduced in 1950 when Alan Turing first explained the idea of simulating intelligent behaviour and critical thinking using computer.[5] Early models had several flaws that impeded widespread adoption and medical use.[6] Gunn first researched the use of AI technology in surgery in 1976, when he explored the possibilities of using computer analysis to diagnose sudden abdominal pain. Interest in medical AI has increased during the past two decades.[1]

The virtual and physical domains are where AI is primarily used. The virtual programme uses mathematical techniques to simulate machine learning, commonly referred to as deep learning, which improves learning *via* experience. The three categories of machine learning algorithms include unsupervised (capable of recognising patterns), supervised (employing prior examples for classification and prediction) and reinforcement learning (forming strategies through rewards and penalties within a specific problem domain). It also has electronic medical records that use specific algorithms to find people who have a family history of a hereditary condition or who are at higher risk of developing chronic diseases.[7]

AI can utilise algorithms to "learn" features from a significant amount of healthcare data and use these discovered insights to improve clinical practice. The accuracy of the system can be enhanced by providing it with learning and self-correcting capabilities based on feedback.[1] Its physical application involves physical items, medical equipment and progressively sophisticated robots participating in the provision of treatment (carebots).[7]

With the help of AI, healthcare is undergoing a paradigm shift, owing to the expansion of healthcare data availability and the quick development of analytical tools.[8] According to estimates, AI will have a profound impact on social and economic systems worldwide.[9]

Surgical management with AI

Advances in surgery have altered the treatment of both acute and chronic illnesses, increasing patient survival rates and lengthening patients' lives. Continuous technical innovations in diagnosis, imaging and surgical instrumentation support these advancements.[10] AI for preoperative planning, surgery effectiveness depends on preoperative planning, in which doctors design the surgical operation based on already-existing medical information and imaging. The most popular imaging techniques utilised in clinical settings are X-rays, CT scans, ultrasounds and magnetic resonance imaging (MRIs). Anatomical categorisation, detection, segmentation and registration are common tasks based on medical imaging.[10] AI for intraoperative guidance is used in shape instantiation, tissue tracking, endoscopic navigation and augmented reality.[10] AI for surgical robotics, the goal of AI is to increase the surgical robotic system's ability to recognise complex *in vivo* circumstances, make judgements and complete the necessary tasks more precisely, safely and effectively.[10] Robotically assisted surgery was created to boost surgeon capabilities and to get beyond the drawbacks of existing minimally invasive surgical techniques.[11]

Orthognathic surgical treatment

Surgery requires precise planning to achieve the appropriate stability and harmony.[12] In order to treat obstructive sleep apnoea (OSA), malocclusion and issues with the facial profile, orthognathic surgery is frequently used in craniofacial surgery. The focus of orthognathic surgery is repositioning the maxilla, mandible and chin.[13] It not only enhances fundamental abilities like chewing, speaking and swallowing, but it also forms a component of a comprehensive plan of care for improving quality of life.[14]

Approaches for early orthognathic surgery

Conventional approach

It is known as the orthodontic first approach. Orthognathic surgery traditionally requires significant pre-operative and post-operative orthodontics to achieve significant dentofacial correction.[15] Before undergoing orthognathic surgery, patients receive preoperative orthodontic therapy to reveal the actual skeletal discrepancies and align the maxilla and mandible for a stable surgical occlusion, thereby preventing postoperative occlusal instability. Despite these advantages, preoperative orthodontic treatment comes with

CONTENT

notable drawbacks, leading to considerable inconvenience for patients. Dental decompensation involves a gradual decline in the facial cosmetic profile and dental function during the preoperative period. Preoperative orthodontic treatment's biggest weakness is that it takes a long time to complete; depending on how complicated the patient's initial dental condition was, to begin with, it can even take up to 48 months.[13]

Surgery-first approach (SFA)

Also referred to as the "surgery-first-orthognathic-approach (SFOA)". The term "surgery-first approach" refers to a course of therapy that begins with orthognathic surgery and ends with postoperative orthodontics without first undergoing preoperative orthodontics. SFOA may be enforced using 2 methods: the surgical driven approach and also the orthodontic driven approach. In the first method, surgical correction is used to treat both dental and jaw abnormalities. The latter method involves surgically correcting jaw distortion and using orthodontics to cure dental deformity. The modified-surgery technique is used when preoperative orthodontic therapy lasts for less than six months.[13, 16] The reduced treatment duration has been a key factor in the prevalence of surgery-first orthognathic,[17] another advantage is the improvement in facial profile right away from starting of the treatment, high levels of patient and orthodontist satisfaction are related to better cooperation during postoperative orthodontics and quick patient recovery.[18]

While the orthodontics-first approach suggests that orthodontic therapy begins first, followed by orthognathic surgery, the surgery-first strategy states that orthognathic surgery begins first.[19] Orthodontics alone can address minor dentoskeletal discrepancies, but for more severe and significant disparities, a combination of orthodontic treatment and orthognathic surgery becomes essential for effective and comprehensive management. Orthognathic surgery can be performed as a single-jaw therapy in which just the maxilla or the mandible is operated on, but bimaxillary (or double-jaw) orthognathic surgery must be planned when the diagnostic information and presurgical planning indicate that both jaws need to be osteotomised.[20, 21]

Surgical planning by virtual surgery technology with its opportunities

A method of merging "computer-aided design (CAD)" and "computer-aided manufacture (CAM)" in surgical treatment planning is known as virtual surgery, also referred to as computer-aided surgery. AI empowers surgeons to optimise skeletal alignments, strategize surgeries for both soft and hard tissues and visualise and evaluate three-dimensional (3D) images of soft tissue and skeletal structures. It also allows surgeons to communicate the virtual plan to patients before the procedure.[22] The science of virtual reality involves building an artificial environment to evaluate different body parts' anatomical regions. This can be useful for diagnosis, planning and surgical training.[23]

Virtual surgery typically comprises four stages. Phase 1 is the data collection it includes radiographic examinations and CT scans, as well as clinical examinations with bite registrations and anthropometric measurements. Phase 2 is the planning phase that involves transferring 3D cone beam computed tomography (CBCT) data into specialised planning software. Phase 3 is the surgical phase, it involves translating the digital surgical plan to the patient using stereolithographic models, occlusal splints, cutting guide stents, or intraoperative navigation. Phase 4 the assessment phase, involves employing intraoperative or postoperative CT imaging to assess the precision of virtual surgical plan transfer.[22] By improving the depiction of 3D phenotypic changes, virtual surgical planning has made it easier to make precise diagnoses and thorough treatment plans. Due to these benefits, intraoperative osteotomies and fixation have increased osteotomy accuracy and considerably reduced preoperative surgical planning.[13] CBCT scan is preferred for 3D scan, CBCT is a method for acquiring medical images and a cone-shaped X-ray beam is focused on a two-dimensional (2D) detector. Two CBCT scans were collected using the "i-CATTM equipment, version 17-19 (*Imaging Sciences International*, Hatfield, PA, USA)" one preoperative (taken two months before orthognathic surgery) and one postoperative (taken one month after surgery).[24]

Orthognathic surgery falls under the scope of oral and maxillofacial surgery and orthodontics that tries to correct dentofacial defects by moving the maxillomandibular complex into a more functional, balanced and aesthetically acceptable posture. Because of the procedure's complexity, the accuracy of surgical planning is essential. The adoption of 3D virtual planning techniques and the creation of prototyped splints are made

CONTENT

possible by developments in imaging, planning software and prototyping technology. In order to better understand the link between the dental arches and the surrounding bones, virtual surgical planning (VSP) provides new opportunities. When compared to traditional surgical planning, this method offers several benefits, including the ability to visualise deformities and asymmetries that are occasionally missed, the freedom to simulate various surgical procedures to achieve the best possible patient outcomes, the ability to identify potential complications and simplicity in assessing and adjusting the centric relation in the temporomandibular joint.[25] At the end of the 1980s, 3D virtual planning software packages with virtual operating rooms (VOR) were introduced. Significant advancements in these software modules have been made possible by the IT revolution (2000s). The doctor can document, analyse and plan orthognathic surgery using a face skeleton model due to the reconstruction of "digital imaging and communications in medicine (DICOM)" files in a VOR. Dental models and software to analyse the soft tissue surface of the face's soft tissues were also introduced.[26] A preintervention survey is performed to evaluate training requirements and a postintervention feedback survey to assess the system's effectiveness, usability and acceptability was utilised to assess the validity of VR surgery.[27] Because of technological advances, particularly 3D printing and VSP, this field has grown and improved significantly. The advancement has significantly enhanced preoperative preparation, leading to a more streamlined journey from pre-surgery to post-surgery. While patients might incur extra expenses, the benefits include reduced operative duration and shorter hospitalisation periods. Future research could concentrate on a cost-benefit analysis to determine whether virtual planning reduces total health-care costs.[7] VSP has proven to be accurate and results in better clinical outcomes as compared to the traditional model surgery.[28] Both the traditional and the new 3D virtual method operate on the same principles. The objective remains to provide the greatest possible outcome for improved patient care.[29]

Implementation of AI software in orthognathic surgical planning

The surgical approach employed and the precision with which the surgical plan is carried out determine how well an orthognathic procedure goes. Two crucial and fast developing topics of study are virtual planning and computer-assisted surgery. Computer-assisted surgery (CAS) is the practise of performing or planning surgery with the aid of cutting-edge technology. The use of software analysis, virtual planning, sophisticated imaging fast prototyping technologies, robotics and image guiding systems are some examples of these techniques.[30] Hirsch first made CAS for mandibular reconstruction available in 2009. Since then, it has become more and more popular. The terms fast prototyping "computer-aided design" and "computer-aided manufacturing" are also used to describe it.[31] For orthognathic (jaw realignment) and temporomandibular joint (TMJ) surgery, facial trauma, implantology (dental implants) and maxillomandibular reconstruction, craniofacial surgery (CMF) and dentistry currently use CAS most frequently.[32] After a model operation is designed, the production of surgical splints on dental casts is the most common method for transferring the desired new relationship of the jaws.[33]

There are a variety of software programmes for CAS and some of them enable internal CAS to be carried out using database images (CBCT, intraoral scans) and with the creation of a surgical splint it is then transferred to the operating room.[34] Few software available for planning of orthognathic surgery are enlisted in Table 1, which include the *Dolphin imaging* (version 11.9, California, USA),[35-37] *Dolphin imaging* (11.95, USA),[38] *Proplan CMF* (Leuven, Belgium),[35, 39-42] *Proplan CMF* (Materialise CMF, USA),[43] *ITK-SNAP* (3.4.0, USA),[44, 45] *Dentofacial Planner Plus* (USA),[36, 37, 46-48] *SurgiCase* (5.0, Belgium),[49] *SurgiCase-CMF PRO 1.2* (USA),[50] *3-matic* (Belgium),[50-52] *3D Slicer* (4.5.0-1, USA),[45, 53, 54] *OrthoGnathicAnalyser (2.0)*,[55, 56] *Maxilim* (Belgium),[39, 55, 57, 58] *IPS CaseDesigner* (2.0.4.2, Germany),[37, 59] *VRMesh* (USA),[59, 60] *NemoFab* (Spain)[61, 62] and *Autodesk MeshMixer* (USA).[35, 61] *Dolphin 3D imaging* software helps to enable CBCT volumes to be oriented and selectively cropped and allows linear measurements of the joint space and volumetric analysis of changes in condylar volume.[63, 64] The "Houston Methodist Research Institute's Surgical Planning Laboratory" has created a computer aided surgical simulation (CASS) protocol tailored specifically for orthognathic surgery. The CASS protocol is discussed below in detail. There is a modified CASS method that uses extraoral photographs in the natural head position (NHP) taken with a camera's built-in gyroscope to achieve the same accuracy as the regular CASS method.[65]

CONTENT

CBCT images were taken prior and post orthognathic surgery for the assessment of mandibular anatomy and position. CBCT images have revolutionised orthodontics by computer-aided surgical simulations and has been adapted for use in orthognathic surgery to make cephalometric analysis, surgical simulation and splint fabrication easier.[64, 66] CBCT scanners produce high-resolu-

Table 1: Software for orthognathic surgery planning

Software	Version	Country	Data	Statistical analysis	Application	Ref.
Proplan CMF	-	Belgium	Each patient had cone-beam CT scanning and using STL format the scanned data is imported into the software.	Paired t-test	Generate 2D or 3D visualisations, preoperative testing, analyse postoperative results and refine surgical plans.	35, 39-43
Dentofacial Planner Plus	-	USA	Compared with CBCT scan of initial one of the patients.	Chi-square test, ANOVA and the Tukey test	Profile analysis, treatment prediction and predict the postsurgical profiles.	36, 37, 46-48
Dolphin Imaging	11.9	USA	It uses an algorithm based on sparse landmarks to predict soft tissue outcomes, offering the flexibility to adjust hard-to-soft tissue ratios to accommodate variations among different patients.	Friedman test	Predict the postsurgical profiles and changes with a primary focus on the 2D midline and upper lip.	35-37
	11.95	USA	Lateral cephalograms, horizontal measurement, vertical measurement and 3 angular measurements of the patients was analysed.	Student's t-test	Assessing skeletal changes post orthognathic surgery.	38
Surgi Case	5	Belgium	CAS was performed on patients with an average age of 35.5 years and CT of the maxillofacial skeleton and lower extremities were performed.	-	Evaluation of orthognathic surgical outcomes and accuracy	49
	CMF PRO 1.2	USA	Preoperative multi-slice imaging data were acquired using a CT unit, stored in DICOM format. It uses a physically based, previously published simulation module.	M, SD, SE, Max, 90th and 95th percentile	Used to calculate postoperative simulation of the soft tissue and helps to simulate any movement.	50
3-matic	-	Belgium	Data is collected through CBCT scan of patients, the software allows for various analyses and simulations on the patient's 3D models.	Student's t-test	This software serves as a preprocessing tool, enabling users to perform tasks such as repairing, preparing geometry, remeshing and making design modifications directly on the mesh data.	50-52
ITK-SNAP	3.4.0	USA	Before the surgical procedure, all the participants underwent preoperative scanning for virtual surgical planning and follow-up scans were performed one week later.	STATA 14.2	This tool is utilised for the segmentation of structures in three-dimensional (3D) and four-dimensional (4D) biomedical images.	44, 45
3D Slicer	4.5.0-1	USA	CBCT scan of patients.	STATA 14.2	The software is designed for visualising, processing, segmenting, registering and analysing medical, biomedical and other 3D images and meshes. Additionally, it facilitates the planning and navigation of image-guided procedures.	45, 53, 54

CONTENT

Ortho Gnathic Analyser	2	-	Using six confirmed cephalometric landmarks, the 3D augmented virtual head model was placed in its anatomically natural position before the surgery.	IBM SPSS software	Analyse and improve 3D planning accuracy in bimaxillary surgery.	55, 56
Maxilim	-	Belgium	CBCT scan of patients.	IBM SPSS software	This tool is employed to create a 3D virtual head model with augmented features.	39, 55, 57, 58
IPS Case Designer	2.0.4.2	Germany	CBCT scan of patients.	t-test	Wizard-based approach for case setup and planning, Real-time soft tissue simulation, 3D Cephalometric analysis.	37, 59
VRMesh	-	USA	The models are scanned using an intraoral scanner and then imported into VRMesh in the stereolithography (.stl) format.	One-sample Student t-test	Used to evaluate the real time quality of the occlusions.	59, 60
NemoFab	-	Spain	CBCT scan of patients.	-	Surgical planning software.	61, 62
Autodesk Meshmixer	-	USA	CBCT scan of patients.	-	Enables the surgeon to precisely analyse and strategize the surgical procedure and is capable of performing Boolean operations.	35, 61

ANOVA: analysis of variance; M: mean; SD: standard deviation, SE: standard error of mean; CBCT: cone beam computed tomography; CAS: computer-assisted surgery; DICOM: digital imaging and communications in medicine; Ref.: reference number;

tion images while using less radiation than spiral CT scanners. In order to assess the complex dentofacial structures, 3D CBCTs are the preferred technique. The limitations of the two-dimensional quantitative and qualitative evaluation of surgical displacements can be overcome by using cone-beam computed tomography and three-dimensional imaging technologies.[67, 68] There are numerous reported uses for CBCT in the fields of orthodontics and maxillofacial surgery, including the identification of impacted teeth and the evaluation of implant sites.[69] Postoperative CBCT imaging was taken within 4 weeks of the surgery.[70]

CASS protocol

Through the use of CASS software, orthognathic surgery's effectiveness and precision in treating dentofacial deformity have been greatly increased.[71] CASS clinical implementation entails the following four steps: 1) gathering preoperative information, 2) data processing, 3) surgical planning and 4) plan execution itself. Typically, a surgeon handles the first and third processes; however, the other two might be delegated to a specialist or an independent service provider.[72]

Preoperative data collection

Preoperative data are acquired in this stage during an hour-long session. Eight steps make up this appointment: (1) taking dental impressions; (2) bite-jig fabrication; a patient-specific bite-jig is created by adapting a stock jig frame to fit the patient's teeth. The number of impressions required for the planning process depends on the type of surgery (Figure 1). Until the fabric is cured, the jig is maintained in place between the patient's teeth. This bite registration should be taken in centric relation (Figure 2). (3) Clinical measures are taken and the measurements required for clinical planning are noted. The following are some examples: (a) "rest-incisal-show" and "smile-dentogingival-show", which are used to determine the maxilla's vertical position; (b) dental midpoint (midline) deviations, which are used to determine the position of the transverse jaw; and (4) clinical photography, in which the patient's face and teeth are captured on camera. Facial images should be shot with the patient in the NHP position and a plumb line in the backdrop so that the proper alignment of the face may be confirmed afterwards. (5) Recording the patient's NHP, which is necessary for the creation of an anatomical reference frame. The goal of these photographs is to confirm that the virtual head model is correctly oriented for planning. A bite-jig is put between the patient's teeth and has a sensor attached to it. It is requested that the patient stand straight and place their head in NHP. Lastly, while in this position, the sensor's pitch, roll and yaw

CONTENT

are recorded; (6) confirming that the models and the bite-jig are accurate by testing the fit of the stone dental models on the bite-jig, which is done by a surgeon or an assistant; (7) after obtaining a CT scan, or ideally a CBCT scan, the patient is fastened to the bite-jig, which is then attached to the fiducial registration face-bow. The patient is told to maintain relaxation in his or her facial soft tissues while being scanned.[72]

Data processing

The procedure may be carried out by the surgeon, a third-party service provider, or a member of the clinic or institution who is knowledgeable about CASS planning. The procedures for processing data consist of; (1) construction of a virtual model of a composite head - the first stage is to create a model that accurately depicts the teeth, soft tissues and skeleton. The midface model, soft tissue model, mandibular model and fiducial marker model are four distinct and correlated 3D-CT models that are created. (2) Using the fiducial face-bow as a reference, an anatomical reference frame is created for the head model and the NHP of the computer model is created by utilising the recorded roll, pitch and yaw to the face-bow frame. (3) Digitisation of all cephalometric landmarks and completing a cephalometric analysis are regarded to be essential diagnostic procedures for identifying the most effective therapy approach.[5] Any sort of cephalometric analysis can be requested by the surgeon, but he or she should be aware that 3D cephalometry is significantly more complicated than 2D cephalometry. (4) Creating the virtual osteotomies - carry out virtual genioplasty, Le Fort I osteotomies and mandibular ramus osteotomies eg; establishing the final occlusion. (5) The final occlusion that the surgeon chose is etched on the stone dental models. This stone models are initially converted into the final occlusion using the surgeon's generated bite registration. The models are then all simultaneously scanned with either a high-resolution optical surface scanner or a CBCT scanner. After segmenting the scan, a 3D image of the upper and lower teeth in their final occlusion is produced. The "final-occlusal-template," as the produced image is known, is loaded into the planning tool and used as a guide to articulate the jaws in final occlusion. Positioned in line with the upper teeth of the "Le Fort I" segment are the upper teeth of the final occlusal template. After that, the distal mandibular segment is adjusted so that the lower teeth line up with those of the template. The template can be aligned to one jaw, then the other jaw to the template because the template's upper and lower teeth are in final occlusion. This will automatically align both jaws into final occlusion.[72,73]

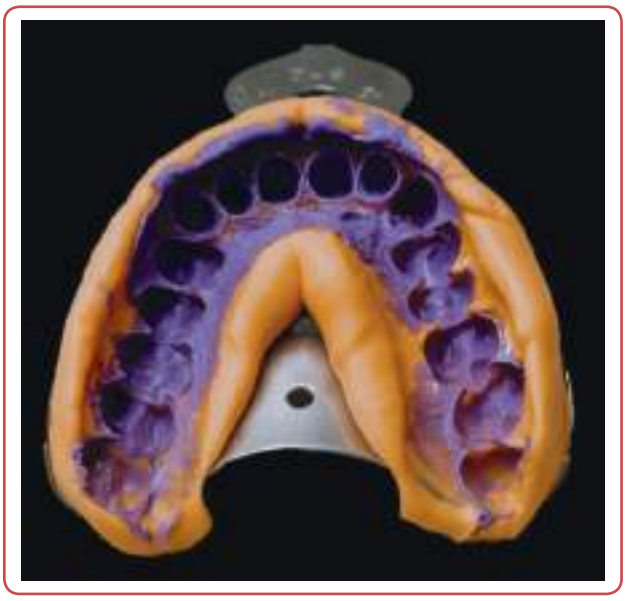


Figure 1: Computer aided surgical simulation (CASS) protocol - bite-jig model

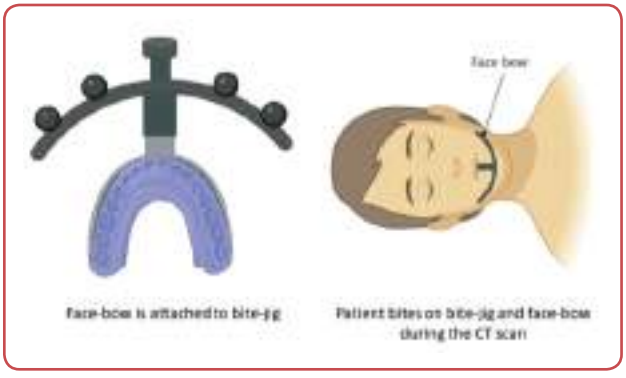


Figure 2: Computer aided surgical simulation (CASS) protocol - patient employing bite-jig

Surgical planning

Using CASS software, this is accomplished on a computer. A surgeon can complete the process alone or with the help of a planning professional familiar with the programme (Figure 3). To make sure that the data processing is accurate, the planning process starts with a checklist. The following items are included on the checklist: (1) Is the anatomical reference frame defined correctly? (2) Have all of the cephalometric landmarks been accurately digitalised? (3) Are all virtual

CONTENT

osteotomies correct? (4) Is the final occlusion accurate? Even when mandibular surgery is performed initially, the maxilla should always be the first part of the CASS planning for any double-jaw surgery. This is because the surgeon is more confident where the maxilla should be positioned than the mandible.[72]

The first step in correcting maxillary abnormalities is to verify the alignment of the teeth symmetrically with respect to the midsagittal plane. Three transformations are necessary for symmetric alignment, including normalising transverse position. The maxillary incisal midpoint is transversely translated onto the midsagittal plane, normalising roll. (1) Roll rotation pivots the maxilla around the incisal midpoint, normalising yaw rotation, which pivots the maxilla around the incisal midpoint. (2) Normalisation of vertical position: The maxilla's vertical position is adjusted. The planner adjusts the maxilla forward or downward to place the incisal midpoint optimally in relation to the upper lip stomion. (3) Pitch normalisation - maxillary pitch is adjusted. The planner adjusts the maxilla's pitch by rotating it around the incisal halfway. Maxillary pitch rotation affects the size of the airway, the projection of the anterior nasal spine, the projection of the chin, the inclination of the maxillary central incisors and the inclination of the maxillary occlusal plane. All of these factors must be taken into account when determining the best maxillary pitch for a particular patient. (4) By aligning the maxilla in anteroposterior position, the anteroposterior position is normalised. This correction is performed last since earlier changes could have an impact on how far the maxilla is advanced.[72]

Additionally, it involves aligning the proximal regions of the jaw and correcting mandibular abnormalities, rotation of each proximal segment about the axis of its condyle to align it.[72] Then, chin deformities must be corrected. This assessment is crucial because the movement of the mandibular distal segment changes the position of the chin. Planning progresses to the last phase. In both cases, the planner should execute a genioplasty by changing the chin piece until the outcomes are satisfied, depending on whether the chin is normal or incorrect.[72]

Finally, with the aid of the planner, the residual final symmetry is examined. In improperly symmetric mandibles, symmetry is preserved by putting the distal mandible in final occlusion. The patient's intrinsic mandibular asymmetry could not be fixed even after the distal jaw is brought into final occlusion. Finishing a final symmetry assessment on every patient is crucial since low to moderate degrees of inherent asymmetry could not be obvious to the eye.[72]

Preparation for plan execution

Preparation of the tools required at the time of the surgery for transferring the computerised surgical plan to the patient is the last step of the CASS protocol. Usually, a third-party service provider is hired to handle this. The tables and graphics that show the intended movements, including mapped areas of collision, are created and displayed during surgery to direct the procedure.[72]

The implementation of VSP with CASS has significantly enhanced the accuracy and efficiency of orthognathic surgery for dentofacial deformity correction. The use of technology has allowed for improved preoperative planning, resulting in better outcomes for patients.

Challenges encountered during surgery

Major challenges faced during orthognathic sur-

Figure 3: Orthognathic surgery plan using computer aided surgical simulation (CASS)

CONTENT

gery are: (a) Patient age in relation to surgical timing - the skeletal repositioning component of orthognathic therapy is often performed after the majority of face growth has taken place. When a patient is ready for surgery, skilled teams frequently start orthodontic preparation therapy at an age at which they are unlikely to have any considerable remaining growth potential. There is a lack of information regarding the ideal time to do surgery on patients who are still growing and it is unclear how such surgery may affect subsequent growth.[74] The other big challenge is (b) psychosocial evaluation - the patient with underlying psychological and/or psychiatric difficulties is one of the biggest hurdles in orthognathic surgery, especially when such problems are not identified until the postoperative period. To overcome such problem every orthognathic team should ideally have a clinical psychologist or liaison psychiatrist who is knowledgeable in the subject to evaluate patients before treatment and as needed throughout therapy. Pre-treatment body dysmorphic disorder (BDD) screening tools, like the "Body Dysmorphic Disorder Questionnaire (BDDQ)", should be a common procedure.[74] Major disadvantage associated with virtual planning can be such that, the 3D virtual treatment planning viewer format requires a good graphically capable personal computer workstation, which is currently not standard. This issue will soon be resolved by the increasing graphic ability in recent commercially accessible personal computers.[75]

Orthognathic surgery-related complications

Despite the fact that the majority of patients undergo orthognathic surgery for cosmetic reasons, postoperative functional issues are more frequently experienced after cosmetic changes. Patients must therefore carefully consider whether having orthognathic surgery will serve an aesthetic or functional goal. The 3D soft tissue alterations after orthognathic surgery have piqued the curiosity of doctors and patients alike.[76]

Orthognathic surgery can result in a wide range of problems. Intraoperative complications include haemorrhage and bad split/segment fractures. When the "inferior alveolar, superior alveolar, maxillary, retromandibular, facial and sublingual vessels" are injured, it might result in severe bleeding. Bad split/segment fractures, like buccal plate fracture, "distal segment lingual fracture" can occur.[77] As the population ages and medical science and technology advances rapidly, health systems around the world are facing immense pressure to provide high-quality care to patients while demand and costs of health services continue to grow.[78] It has observed that with the use of ultrasonic curettage device there is decrease in intraoperative blood loss and calculated blood loss in orthognathic surgery.

Conclusion

Early orthognathic surgery involves the conventional approach also called as the orthognathic first approach and the surgery first approach. In contrast to the orthodontics-first strategy, which means that the orthodontic treatment comes first, the "surgery-first approach" implies that the orthognathic surgery comes first. Virtual surgery, also known as "computer-aided surgery", is a technique that combines CAD and CAM into surgical treatment planning. Virtual surgery involves 4 phases data collection, planning, surgical and assessment. By improving the depiction of 3D phenotypic changes, virtual surgical planning has made it easier to make precise diagnosis and thorough treatment plans. CBCT images should be taken prior and at the end orthognathic surgery for the assessment of mandibular anatomy and position. In order to assess the complex dentofacial structures, 3D CBCTs are the preferred technique. CASS is clinically implemented in 4 steps: collection of preoperative records, data processing, surgical planning and preparing for plan execution. Basic steps are: first the facial photographs are taken with patient in the NHP, creation of virtual model, 3D cephalometry, correction of maxillary, mandibular and chin deformities and transferring the computerised surgical plan to the patient. Patient age and the psychological and/or psychiatric difficulties can be the challenge for surgery. Other challenge is it requires a personal computer workstation with good graphic ability. Haemorrhage and bad split/segment fractures are the various intraoperative complications associated during surgery. To overcome the challenges of early orthognathic surgery and for effective planning of surgery different software are being employed such as *Proplan CMF, Dolphin Imaging, SurgiCase, 3-matic, ITK-SNAP, OrthoGnathicAnalyser* etc. Use of digital tools will have an immense impact on orthognathic-surgical

CONTENT

treatment plans ranging from diagnosis to follow-up treatment. Software has the ability to learn from every real-life case and further improve its performance.

Ethics

This study was a secondary analysis based on the other primary publications and did not directly involve with human participants or experimental animals. Therefore, the ethics approval was not required in this paper.

Acknowledgement

We are thankful to Shobhaben Pratapbhai Patel School of Pharmacy and Technology Management, SVKM's NMIMS for providing the facility.

Conflicts of interest

The authors declare that there is no conflict of interest.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Data access

The data that support the findings of this study are available from the corresponding author upon reasonable individual request.

Author ORCID numbers

Anju Sharma (AS):
0009-0006-9905-0199
Ginpreet Kaur (GK):
0000-0002-5151-914X
Hardeep Singh Tuli (HST):
0000-0003-1155-0094
Raunak Singh Chhabra (RSC):
0009-0000-9145-3264
Rashmi Rana (RR):
0000-0003-1461-9456

Author contributions

Conceptualisation: AS, GK
Methodology: AS, GK
Investigation: AS, RR, HST, RSC
Writing - original draft: AS, RR, HST, RSC
Writing - review and editing: GK, RSC, HST, RR
Visualisation: AS, GK
Supervision: AS, GK

References

1. Scerri M, Grech V. Artificial intelligence in medicine. Early Hum Dev. 2020 Jun;145:105017. doi: 10.1016/j.earlhumdev.2020.105017.
2. Howard J. Artificial intelligence: Implications for the future of work. Am J Ind Med. 2019 Nov;62(11):917-26. doi: 10.1002/ajim.23037.
3. Yu KH, Beam AL, Kohane IS. Artificial intelligence in healthcare. Nat Biomed Eng. 2018 Oct;2(10):719-31. doi: 10.1038/s41551-018-0305-z.
4. Mohammad-Rahimi H, Nadimi M, Rohban MH, Shamsoddin E, Lee VY, Motamedian SR. Machine learning and orthodontics, current trends and the future opportunities: A scoping review. Am J Orthod Dentofacial Orthop. 2021 Aug;160(2):170-92.e4. doi: 10.1016/j.ajodo.2021.02.013.
5. Kaul V, Enslin S, Gross SA. History of artificial intelligence in medicine. Gastrointest Endosc. 2020 Oct;92(4):807-12. doi: 10.1016/j.gie.2020.06.040.
6. Muthukrishnan N, Maleki F, Ovens K, Reinhold C, Forghani B, Forghani R. Brief history of artificial intelligence. Neuroimaging Clin N Am. 2020 Nov;30(4):393-9. doi: 10.1016/j.nic.2020.07.004.
7. Jandali D, Barrera JE. Recent advances in orthognathic surgery. Curr Opin Otolaryngol Head Neck Surg. 2020 Aug;28(4):246-50. doi: 10.1097/MOO.0000000000000638.
8. Jiang F, Jiang Y, Zhi H, Dong Y, Li H, Ma S, et al. Artificial intelligence in healthcare: past, present and future. Stroke Vasc Neurol. 2017 Jun 21;2(4):230-43. doi: 10.1136/svn-2017-000101.

CONTENT

9. Uribe FA, Farrell B. Surgery-first approach in the orthognathic patient. Oral Maxillofac Surg Clin North Am. 2020 Feb;32(1):89-103. doi: 10.1016/j.coms.2019.08.009.
10. Zhou XY, Guo Y, Shen M, Yang GZ. Application of artificial intelligence in surgery. Front Med. 2020 Aug;14(4):417-30. doi: 10.1007/s11684-020-0770-0.
11. Hamet P, Tremblay J. Artificial intelligence in medicine. Metabolism. 2017 Apr;69S:S36-S40. doi: 10.1016/j.metabol.2017.01.011.
12. Haas OL Jr, Becker OE, de Oliveira RB. Computer-aided planning in orthognathic surgery-systematic review. Int J Oral Maxillofac Surg. 2014 Nov 25:S0901-5027(14)00430-5. doi: 10.1016/j.ijom.2014.10.025.
13. Seo HJ, Choi YK. Current trends in orthognathic surgery. Arch Craniofac Surg. 2021 Dec;22(6):287-95. doi: 10.7181/acfs.2021.00598.
14. Van Hemelen G, Van Genechten M, Renier L, Desmedt M, Verbruggen E, Nadjmi N. Three-dimensional virtual planning in orthognathic surgery enhances the accuracy of soft tissue prediction. J Craniomaxillofac Surg. 2015 Jul;43(6):918-25. doi: 10.1016/j.jcms.2015.04.006.
15. Naran S, Steinbacher DM, Taylor JA. Current concepts in orthognathic surgery. Plast Reconstr Surg. 2018 Jun;141(6):925e-36e. doi: 10.1097/PRS.0000000000004438.
16. Ahmadvand A, Alavi S, Mehraban SH. An overview of surgery-first orthognathic approach: History, indications and limitations, protocols, and dentoskeletal stability. Dent Res J (Isfahan). 2021 Jun 22;18:47. PMID: 34429867.
17. Sharma VK, Yadav K, Tandon P. An overview of surgery-first approach: Recent advances in orthognathic surgery. J Orthod Sci. 2015 Jan-Mar;4(1):9-12. doi: 10.4103/2278-0203.149609.
18. Peiró-Guijarro MA, Guijarro-Martínez R, Hernández-Alfaro F. Surgery first in orthognathic surgery: A systematic review of the literature. Am J Orthod Dentofacial Orthop. 2016 Apr;149(4):448-62. doi: 10.1016/j.ajodo.2015.09.022.
19. Liou EJ, Chen PH, Wang YC, Yu CC, Huang CS, Chen YR. Surgery-first accelerated orthognathic surgery: orthodontic guidelines and setup for model surgery. J Oral Maxillofac Surg. 2011 Mar;69(3):771-80. doi: 10.1016/j.joms.2010.11.011.
20. Borba AM, Borges AH, Cé PS, Venturi BA, Naclério-Homem MG, Miloro M. Mandible-first sequence in bimaxillary orthognathic surgery: a systematic review. Int J Oral Maxillofac Surg. 2016 Apr;45(4):472-5. doi: 10.1016/j.ijom.2015.10.008.
21. Bouletreau P, Makaremi M, Ibrahim B, Louvrier A, Sigaux N. Artificial intelligence: applications in orthognathic surgery. J Stomatol Oral Maxillofac Surg. 2019 Sep;120(4):347-54. doi: 10.1016/j.jormas.2019.06.001.
22. Gelesko S, Markiewicz MR, Weimer K, Bell RB. Computer-aided orthognathic surgery. Atlas Oral Maxillofac Surg Clin North Am. 2012 Mar;20(1):107-18. doi: 10.1016/j.cxom.2012.01.002.
23. Ayoub A, Pulijala Y. The application of virtual reality and augmented reality in Oral & Maxillofacial Surgery. BMC Oral Health. 2019 Nov 8;19(1):238. doi: 10.1186/s12903-019-0937-8.
24. Vale F, Scherzberg J, Cavaleiro J, Sanz D, Caramelo F, Maló L, et al. 3D virtual planning in orthognathic surgery and CAD/CAM surgical splints generation in one patient with craniofacial microsomia: a case report. Dental Press J Orthod. 2016 Jan-Feb;21(1):89-100. doi: 10.1590/2177-6709.21.1.089-100.oar.
25. Otranto de Britto Teixeira A, Almeida MAO, Almeida RCDC, Maués CP, Pimentel T, Ribeiro DPB, et al. Three-dimensional accuracy of virtual planning in orthognathic surgery. Am J Orthod Dentofacial Orthop. 2020 Nov;158(5):674-83. doi: 10.1016/j.ajodo.2019.09.023.
26. Plooij JM, Maal TJ, Haers P, Borstlap WA, Kuijpers-Jagtman AM, Bergé SJ. Digital three-dimensional image fusion processes for planning and evaluating orthodontics and orthognathic surgery. A systematic review. Int J Oral Maxillofac Surg. 2011 Apr;40(4):341-52. doi: 10.1016/j.ijom.2010.10.013.
27. Pulijala Y, Ma M, Pears M, Peebles D, Ayoub A. An innovative virtual reality training tool for orthognathic surgery. Int J Oral Maxillofac Surg. 2018 Sep;47(9):1199-205. doi: 10.1016/j.ijom.2018.01.005.
28. Farrell BB, Franco PB, Tucker MR. Virtual surgical planning in orthognathic surgery. Oral Maxillofac Surg Clin North Am. 2014 Nov;26(4):459-73. doi: 10.1016/j.coms.2014.08.011.
29. Quevedo LA, Ruiz JV, Quevedo CA. Using a clinical protocol for orthognathic surgery and assessing a 3-dimensional virtual approach: current therapy. J Oral Maxillofac Surg. 2011 Mar;69(3):623-37. doi: 10.1016/j.joms.2010.11.009.
30. Stokbro K, Aagaard E, Torkov P, Bell RB, Thygesen T. Virtual planning in orthognathic surgery. Int J Oral Maxillofac Surg. 2014 Aug;43(8):957-65. doi: 10.1016/j.ijom.2014.03.011.
31. van Baar GJC, Forouzanfar T, Liberton NPTJ, Winters HAH, Leusink FKJ. Accuracy of computer-assisted surgery in mandibular reconstruction: A systematic review. Oral Oncol. 2018 Sep;84:52-60. doi: 10.1016/j.oraloncology.2018.07.004.
32. Landaeta-Quinones CG, Hernandez N, Zarroug NK. Computer-assisted surgery: applications in dentistry and oral and maxillofacial surgery. Dent Clin North Am. 2018 Jul;62(3):403-20. doi: 10.1016/j.cden.2018.03.009.
33. Zizelmann C, Hammer B, Gellrich NC, Schwestka-Polly R, Rana M, Bucher P. An evaluation of face-bow transfer for the planning of orthognathic surgery. J Oral Maxillofac Surg. 2012 Aug;70(8):1944-50. doi: 10.1016/j.joms.2011.08.025.
34. Elnagar MH, Aronovich S, Kusnoto B. Digital workflow for combined orthodontics and orthognathic surgery. Oral Maxillofac Surg Clin North Am. 2020 Feb;32(1):1-14. doi: 10.1016/j.coms.2019.08.004.
35. Knoops PGM, Borghi A, Breakey RWF, Ong J, Jeelani NUO, Bruun R, et al. Three-dimensional soft tissue prediction in orthognathic surgery: a clinical comparison of Dolphin, ProPlan CMF, and probabilistic finite element modelling. Int J Oral Maxillofac Surg. 2019 Apr;48(4):511-8. doi: 10.1016/j.ijom.2018.10.008.
36. Soheilifar S, Soheilifar S, Afrasiabi Z, Soheilifar S, Tapak L, Naghdi N. Prediction accuracy of Dolphin software for soft-tissue profile in Class I patients undergoing fixed orthodontic treatment. J World Fed Orthod. 2022 Feb;11(1):29-35. doi: 10.1016/j.ejwf.2021.10.001.
37. Piombino P, Abbate V, Sani L, Troise S, Committeri U, Carraturo E, et al. Virtual surgical planning in orthognathic surgery: two software platforms compared. Appl Sci. 2022 Sep 19;12(18):9364. doi: 10.3390/app12189364.
38. Thet PH, Kaboosaya B. Reproducibility of computerized cephalometric analysis software compared with conventional manual tracing for analyzing skeletal

CONTENT

stability after orthognathic surgery. J Maxillofac Oral Surg. 2023 Dec;22(4):833-40. doi: 10.1007/s12663-023-02071-7.
39. Lee KJC, Tan SL, Low HYA, Chen LJ, Yong CW, Chew MT. Accuracy of 3-dimensional soft tissue prediction for orthognathic surgery in a Chinese population. J Stomatol Oral Maxillofac Surg. 2022 Oct;123(5):551-5. doi: 10.1016/j.jormas.2021.08.001.
40. Wu Y, Chen JM, Xie FP, Liu HH, Niu G, Lin LS. Simulation of postoperative occlusion and direction in autotransplantation of teeth: application of computer-aided design and digital surgical templates. Br J Oral Maxillofac Surg. 2019 Sep;57(7):638-43. doi: 10.1016/j.bjoms.2019.05.011.
41. Lu C, Xie Q, He D, Yang C. Stability of orthognathic surgery in the treatment of condylar osteochondroma combined with jaw deformity by CT measurements. J Oral Maxillofac Surg. 2020 Aug;78(8):1417.e1-1417.e14. doi: 10.1016/j.joms.2020.03.025.
42. Chen K, Zhang Z, Jiang J, Wang J, Wang J, Sun Y, et al.. Prediction of condylar movement envelope surface based on facial morphology. Heliyon. 2023 Jul 7;9(7):e17769. doi: 10.1016/j.heliyon.2023.e17769.
43. Zavattero E, Romano M, Gerbino G, Rossi DS, Giannì AB, Ramieri G, et al. evaluation of the accuracy of virtual planning in orthognathic surgery: a morphometric study. J Craniofac Surg. 2019 Jun;30(4):1214-20. doi: 10.1097/SCS.0000000000005355.
44. Tran Duy TD, Jinnavanich S, Chen MC, Ko EW, Chen YR, Huang CS. Are signs of degenerative joint disease associated with chin deviation? J Oral Maxillofac Surg. 2020 Aug;78(8):1403-14. doi: 10.1016/j.joms.2020.03.019.
45. Stokbro K, Thygesen T. A 3-dimensional approach for analysis in orthognathic surgery-using free software for voxel-based alignment and semiautomatic measurement. J Oral Maxillofac Surg. 2018 Jun;76(6):1316-26. doi: 10.1016/j.joms.2017.11.010.
46. Magro-Filho O, Magro-Ernica N, Queiroz TP, Aranega AM, Garcia IR Jr. Comparative study of 2 software programs for predicting profile changes in Class III patients having double-jaw orthognathic surgery. Am J Orthod Dentofacial Orthop. 2010 Apr;137(4):452.e1-5; discussion 452-3. doi: 10.1016/j.ajodo.2009.02.027.
47. Gimenez CM, Bertoz FA, Gabrielli MA, Magro Filho O, Garcia I, Pereira Filho VA. Cephalometric evaluation of the predictability of bimaxillary surgical-orthodontic treatment outcomes in long face pattern patients: a retrospective study. Dental Press J Orthod. 2013 Sep-Oct;18(5):53-8. doi: 10.1590/s2176-94512013000500010.
48. Xiao Z, Chen G, Zhao Y, Wang Y, Gu Y. Perceptual difference of smile aesthetics between 2-dimensional photographs and 3-dimensional dentofacial images: a cross-sectional study. BMC Oral Health. 2023 Feb 16;23(1):104. doi: 10.1186/s12903-023-02798-2.
49. Zhang L, Liu Z, Li B, Yu H, Shen SG, Wang X. Evaluation of computer-assisted mandibular reconstruction with vascularized fibular flap compared to conventional surgery. Oral Surg Oral Med Oral Pathol Oral Radiol. 2016 Feb;121(2):139-48. doi: 10.1016/j.oooo.2015.10.005.
50. Marchetti C, Bianchi A, Muyldermans L, Di Martino M, Lancellotti L, Sarti A. Validation of new soft tissue software in orthognathic surgery planning. Int J Oral Maxillofac Surg. 2011 Jan;40(1):26-32. doi: 10.1016/j.ijom.2010.09.004.
51. Karsli N, Yurdakul Z, Gonca M, Çava K. Does the traditional or digital dental model measurement method affect the results?: A validation study. EADS. 2023;50(2):87-94. doi: 10.52037/eads.2023.0021
52. Sürer E, Ünal M, Gül Aygün EB, Ucar Y. Evaluating the conversion degree of interim restorative materials produced by different 3-dimensional printer technologies. J Prosthet Dent. 2023 Oct;130(4):654.e1-e6. doi: 10.1016/j.prosdent.2023.07.001.
53. Trang NT, Ashikaga Y, Matsushita K, Ohiro Y. Investigating the relationship between the remodeling of TMJ bony structures and condylar rest position following orthognathic surgery in class II and class III skeletal malocclusions. J Oral Maxillofac Surg Med Pathol. 2023 Jul 1;35(4):308–16. doi: 10.1016/j.ajoms.2022.12.003
54. Shujaat S, da Costa Senior O, Shaheen E, Politis C, Jacobs R. Visual and haptic perceptibility of 3D printed skeletal models in orthognathic surgery. J Dent. 2021 Jun;109:103660. doi: 10.1016/j.jdent.2021.103660.
55. Baan F, Liebregts J, Xi T, Schreurs R, de Koning M, Bergé S, et al. A new 3D tool for assessing the accuracy of bimaxillary surgery: the OrthoGnathicAnalyser. PLoS One. 2016 Feb 22;11(2):e0149625. doi: 10.1371/journal.pone.0149625.
56. Baan F, Sabelis JF, Schreurs R, van de Steeg G, Xi T, van Riet TCT, et al. Validation of the OrthoGnathicAnalyser 2.0-3D accuracy assessment tool for bimaxillary surgery and genioplasty. PLoS One. 2021 Jan 26;16(1):e0246196. doi: 10.1371/journal.pone.0246196.
57. van Luijn R, Baan F, Shaheen E, Bergé S, Politis C, Maal T, et al. Three-dimensional analysis of condylar remodeling and skeletal relapse following LeFort-I osteotomy: A one-year follow-up bicenter study. J Craniomaxillofac Surg. 2022 Jan;50(1):40-5. doi: 10.1016/j.jcms.2021.09.021.
58. Rozeboom AVJ, Schreurs R, Helmer LML, Dubois L, Lobbezoo F, de Lange J. Volumetric outcomes of treatment for unilateral condylar fractures: A pilot study. Adv Oral Maxillofac Surg. 2023 Mar;9:100399. doi: 10.1016/j.adoms.2023.100399.
59. Almadi D, Benington P, Ju X, Ayoub A. Reproducibility and reliability of digital occlusal planning for orthognathic surgery. Int J Oral Maxillofac Surg. 2023 Oct;52(10):1074-80. doi: 10.1016/j.ijom.2023.03.001.
60. Lin CY, Hsung TC, Khambay B. Reducing cone beam CT scan height as a method of radiation reduction for photorealistic three-dimensional orthognathic planning. J Craniomaxillofac Surg. 2015 Jul;43(6):907-12. doi: 10.1016/j.jcms.2015.04.002.
61. Onică N, Onică CA, Tatarciuc M, Baciu ER, Vlasie GL, Ciofu M, et al. Managing predicted post-orthognathic surgical defects using combined digital software: a case report. Healthcare (Basel). 2023 Apr 25;11(9):1219. doi: 10.3390/healthcare11091219.
62. Yılmaz ZÇ, Özel A, Sağlam R, Uçkan S. Comparison of scleral show alterations following Le Fort I osteotomy with either maxillary impaction or lengthening. J Craniomaxillofac Surg. 2021 May;49(5):347-51. doi: 10.1016/j.jcms.2021.01.031.
63. da Silva RJ, Valadares Souza CV, Souza GA, Ambrosano GMB, Freitas DQ, Sant'Ana E, et al. Changes in condylar volume and joint spaces after orthognathic surgery. Int J Oral Maxillofac Surg. 2018 Apr;47(4):511-7. doi: 10.1016/j.ijom.2017.10.012.
64. Tabchi Y, Zaoui F, Bahoum A. Accuracy of hard and soft tissue prediction using three-dimensional simulation software in bimaxillary osteotomies: A systematic review. Int Orthod. 2023 Dec;21(4):100802. doi: 10.1016/j.ortho.2023.100802.
65. Ferraz FWDS, Iwaki-Filho L, Souza-Pinto GN, Iwaki LCV, Li AT, Cardoso MA. A comparative study of the accuracy between two computer-aided surgical simu-

CONTENT

lation methods in virtual surgical planning. J Craniomaxillofac Surg. 2021 Feb;49(2):84-92. doi: 10.1016/j.jcms.2020.12.002.
66. Alkhayer A, Piffkó J, Lippold C, Segatto E. Accuracy of virtual planning in orthognathic surgery: a systematic review. Head Face Med. 2020 Dec 4;16(1):34. doi: 10.1186/s13005-020-00250-2.
67. Cevidanes LH, Bailey LJ, Tucker GR Jr, Styner MA, Mol A, Phillips CL, et al. Superimposition of 3D cone-beam CT models of orthognathic surgery patients. Dentomaxillofac Radiol. 2005 Nov;34(6):369-75. doi: 10.1259/dmfr/17102411.
68. Motta ATS da, Carvalho F de AR, Oliveira AEF, Cevidanes LHS, Almeida MA de O. [Superposição automatizada de modelos tomográficos tridimensionais em cirurgia ortognática]. Dental Press J Orthod. 2010 Apr;15(2):39–41. Portuguese.
69. Popat H, Richmond S, Drage NA. New developments in: three-dimensional planning for orthognathic surgery. J Orthod. 2010 Mar;37(1):62-71. doi: 10.1179/14653121042885.
70. Wong A, Goonewardene MS, Allan BP, Mian AS, Rea A. Accuracy of maxillary repositioning surgery using CAD/CAM customized surgical guides and fixation plates. Int J Oral Maxillofac Surg. 2021 Apr;50(4):494-500. doi: 10.1016/j.ijom.2020.08.009.
71. Ruggiero F, Borghi A, Bevini M, Badiali G, Lunari O, Dunaway D, et al. Soft tissue prediction in orthognathic surgery: Improving accuracy by means of anatomical details. PLoS One. 2023 Nov 27;18(11):e0294640. doi: 10.1371/journal.pone.0294640.
72. Xia JJ, Gateno J, Teichgraeber JF, Yuan P, Chen KC, Li J, et al. Algorithm for planning a double-jaw orthognathic surgery using a computer-aided surgical simulation (CASS) protocol. Part 1: planning sequence. Int J Oral Maxillofac Surg. 2015 Dec;44(12):1431-40. doi: 10.1016/j.ijom.2015.06.006.
73. Xia JJ, Gateno J, Teichgraeber JF, Yuan P, Li J, Chen KC, et al. Algorithm for planning a double-jaw orthognathic surgery using a computer-aided surgical simulation (CASS) protocol. Part 2: three-dimensional cephalometry. Int J Oral Maxillofac Surg. 2015 Dec;44(12):1441-50. doi: 10.1016/j.ijom.2015.06.007.
74. Naini FB, Gill DS. Challenges and opportunities facing contemporary orthognathic surgery. J Orthod. 2019 Jun;46(1_suppl):71-6. doi: 10.1177/1465312519840044.
75. Swennen GR, Mollemans W, Schutyser F. Three-dimensional treatment planning of orthognathic surgery in the era of virtual imaging. J Oral Maxillofac Surg. 2009 Oct;67(10):2080-92. doi: 10.1016/j.joms.2009.06.007.
76. Kau CH, Cronin A, Durning P, Zhurov AI, Sandham A, Richmond S. A new method for the 3D measurement of postoperative swelling following orthognathic surgery. Orthod Craniofac Res. 2006 Feb;9(1):31-7. doi: 10.1111/j.1601-6343.2006.00341.
77. Kim YK. Complications associated with orthognathic surgery. J Korean Assoc Oral Maxillofac Surg. 2017 Feb;43(1):3-15. doi: 10.5125/jkaoms.2017.43.1.3.
78. Kakarala K, Shnayder Y, Tsue TT, Girod DA. Mandibular reconstruction. Oral Oncol. 2018 Feb;77:111-7. doi: 10.1016/j.oraloncology.2017.12.020.

CONTENT

Greš et al. Scr Med. 2024 Mar-Apr;55(2):245-50. DOI:10.5937/scriptamed55-48135

CURRENT TOPIC

Aspects and Dilemmas of Euthanasia in Modern Times

Alen Greš,[1] Dijana Staver,[2] Ljubomir Radovančević[3]

Abstract

Euthanasia is a very complex medical and moral issue. The name has taken throughout history quite different meanings especially in recent decades. There have been many controversial debates and ethical questions raised in modern society. The aim of the paper was to introduce in more detail the issue of euthanasia in the modern world and to review the decisions on this issue. The end of life is still a part of life. It is of great importance for every person and requires true compassion and solidarity. The task is to restore human dignity, by respecting the will of the sedating patient. It is the responsibility of doctors and medical staff to use their comprehensive knowledge and ethical approach to provide calm patients with peace and tranquillity. Euthanasia is a discipline. It is also a concept and a term full of conflicts, which need to be analysed. Therefore, it is necessary to consider the criteria of the bioethical aspect of this activity. The right to euthanasia is not ethically indifferent. We can expect in the near future a deeper understanding of the euthanasia issue.

Key words: Euthanasia; Modern society; End of life; Human dignity; Jurisprudence.

1. Department of Psychiatry and Psychological Medicine, University Hospital Centre Zagreb, Zagreb, Croatia.
2. Neuropsychiatric Hospital "Dr. Ivan Barbot" Popovača, Popovača, Croatia.
3. The Croatian Association for the Promotion of Patients' Rights, Split, Croatia.

Citation:
Greš A, Staver D, Radovančević LJ. Aspects and dilemmas of euthanasia in modern times. Scr Med. 2024 Mar-Apr;55(2):245-50.

Corresponding author:
ALEN GREŠ
E: alengres@gmail.com

Received: 17 December 2023
Revision received: 29 January 2024
Accepted: 30 January 2024

Introduction

"All human life is nothing but a journey to death."
- *Seneca*

The word euthanasia is of Greek origin. The word "eu" means good and the word "Thanatos" means death.[1] When combined etymologically they mean a good, peaceful and gentle death. It was also called "mercy killing", that is when someone cannot be helped in any other way, so that they won't suffer anymore.[2] Consequently, all aspects of euthanasia involve the fields of bioethics and suicidology. Euthanasia has no persistent, nagging clumsy implications as death occurs in calmness and dignity. The imperativeness of legalising euthanasia lies in cases where treatment is futile. Even palliative care in a hospice no longer helps and an individual essentially vegetates, deprived of the social dimension and quality of life. At such a stage, as the priest at the funeral says, such an individual suffers from "death agony" as their soul is in their nose.[3] Although death itself does not have to be painful, a dying person in modern times may be given strong analgesics to alleviate any discomfort. They may also undergo procedures such as injections, preparation of veins for infusion, or transfusions and be connected to medical devices.[4] However, if the person is not unconscious or in a coma (without having been induced), they may still experience some degree of pain and suffering as they approach the end of their life. Despite attempts to manage their pain with various pharmacological interventions, these efforts may prove ineffective and inadequate. Healing cannot be assumed

Copyright © 2024 Greš et al. This is an open access article distributed under the Creative Commons Attribution License (CC BY), which permits unrestricted use, distribution and reproduction in any medium, provided the original work is properly cited.

CONTENT

or predicted, as doctors in the intensive care unit have experienced. Doctors who make predictions about a patient's lifespan, whether it be months or days are disrupting the potential for their survival.[5] This is referred to as *vitium artis*, denying someone's recovery. Additionally, many patients fear being buried alive or in a crematorium. Euthanasia, also referred to as "assisted suicide", is a procedure carried out when an individual is in close proximity to death. A well-known statement by the Greek philosopher goes, "I am not afraid of death - when I am here, it is gone and when it comes, I am gone".[6] Euthanasia can be categorised into three types based on the cause, consent or intention. With respect to the cause, euthanasia can be passive, active, voluntary or involuntary.

Active euthanasia is generally understood to take place in a medical setting and involves intentionally ending a person's life, as well as that of animals.[7] Passive euthanasia, on the other hand, is typically used to refer to the withholding or withdrawal of necessary treatment for the purpose of protecting and preserving human life. This can include decisions to prolong life or to not provide treatment. The moral distinction between active and passive euthanasia is that the former involves causing a person's death, whereas the latter involves allowing them to die.[8]

Voluntary euthanasia incorporates two subterms: it refers to the act of dying at the request of a terminally ill person. Testamentary euthanasia, a type of voluntary euthanasia, is when a person gives instructions on how they want to be treated in the event that they are unable to express their wishes due to illness or injury. It's crucial to note that during times when a patient is unable to communicate their desires, due to a severe illness or trauma, the patient's wishes are of utmost importance.[9]

Involuntary euthanasia refers to the death of an individual who did not consent to it. Such an act is necessarily regarded as criminal homicide. Some patients view death as the natural conclusion to the events of their life. Such individuals are not interested in expediting their death nor are they inclined to delay it. Death, for them, is a mystery that they approach with equanimity.[10] Doctors may deem it necessary to intervene in certain circumstances. Medical science has its limitations. Distinctions exist between active intervention by a doctor to end life and the decision not to prolong life (decision not to treat). Patients may request either course of action, while also having the right to refuse or consent. There are instances in which an individual is unable to make a decision. *Dysthanasia* serves as the antithesis of euthanasia, meaning it is a term that refers to the provision of treatment that is futile and results in a prolonged period of suffering.[11]

Attitudes towards euthanasia vary worldwide when comparing criminal procedures for euthanasia, mercy killing and assisted suicide. It can be inferred that there are divergent legal approaches, particularly in European countries. Patient autonomy is a crucial aspect of informed healthcare and it is most effectively achieved through a relationship of trust and openness between the doctor and patient.[12]

Discussion

"He who fears death will never do anything worth of a man who is alive."
- *Seneca*

Euthanasia throughout history

It was first recorded around three hundred years before Christ. In the Greek literature, euthanasia is a rare term, in the theatre work "Ant" by the Greek comedy writer Posidiopo. In the Roman Empire, according to historians, Cicero was the first who mentions euthanasia. In the Renaissance, under the influence of antiquity, the art of dying "ars moriendi" was developed. In the modern age, during the 18th century, doctors did not agree to euthanise seriously ill patients. In 1903, the New York State Medical Association came out accepting and supporting euthanasia.[13] At the end of the 19th century, euthanasia became more and more topical. A lot of literary works were created on the subject of euthanasia and its problems. During the Second World War, euthanasia "flourished" despite the fact that everything was done secretly and illegally.[14] In 1952, a request was sent to the United Nations (UN) to recognise and approve euthanasia. In 1984 the Congress of the International Association for the Right to Die was organised in Nice. The legalisation of euthanasia has been requested many times, especially often in Great Britain and the USA, but so far the requests have been unsuccessful. In 1976, the Council of Europe adopted the right

CONTENT

of patients not to suffer uselessly. Euthanasia is not approved in Norway and Uruguay, but it is not punishable. Certain forms of euthanasia or assisted suicide are currently legalised in a minority of countries in the world such as: the Netherlands, Belgium, Luxembourg, Switzerland, Australia, New Zealand, Canada, Spain, while palliative sedation is allowed in France.[15]

Hospice and palliative care needs

Other assistance in alleviating pain and suffering in the terminal phase of the disease may be considered in accordance with human dignity. There are institutions that take nursing of patients in the terminal phase of the disease, taking into account their individual needs. Care of terminally ill patients mostly comes down to reducing pain and suffering. Therefore palliative care has also a holistic approach to the patient. The role of the hospice approach is interdisciplinary. Part of caring for the patient also belongs to the family itself.[16] Undisputed values of palliative care and hospice are fundamental assumptions and visible factors in the scope of activities of various centres and in understanding the point of view of providers of services to the dying persons. Everything is interconnected and networked. Candidates for euthanasia actually mostly live on the last, final border of physical life and death. Some can stay that way for a long time.[17] Therefore, death fascinated and worried even primitive people and they tried in many ways to naively prevent, postpone and deny it. In 2014 the World Health Organization Assembly approved a resolution on "Strengthening palliative care as a component of comprehensive care throughout life".[18]

Views of religions on euthanasia

From the Church's point of view, abortion is also euthanasia (not voluntary), by the request and begging of the mother, because according to the dogmatic postulate of the Church, life begins with conception. The mercy of euthanasia, Pope John Paul II. declares it to be false pity, since true pity does not kill, but stands in solidarity with the sufferer.[19] Euthanasia has a controversial history and calls into question the central belief of the Judeo-Christian tradition, which is the "sanctity of human life". Because it is seen as a gift from God, taking a life is forbidden and severely punished. In the eyes of many believers, euthanasia is still a form of a murder. Numerous world religions are currently dealing with the issue of euthanasia.[20]

Dilemmas about euthanasia

Euthanasia as a term itself together with everything it represents becomes the subject of constant and rather controversial discussions. This is the case with every conscious human, who distinguishes "Good from Evil", because he has a superego and an ego.[21]

The mythological-religious-philosophical, psychoanalytical term "Thanatos" is an integral part of the word euthanasia. It is one of the cardinal things, along with the context of freedom, bioethics, ontology, battles, being, epistemology, coexistence and other terms and disciplines. Philosophy cannot avoid such contents that preoccupy euthanasia: desire, freedom, will, plea for a solution to the human final event.[22]

In the past suicide survivors were penalised in some countries. It was forbidden to bury suicide victims on the consecrated soil of the cemetery. Antigone's concern for her brother's burial is a striking ancient example. By suicide, the state (society) is deprived of its member in which it was invested from the Church of it benefactors and procreation believers. The legalisation of euthanasia is not allowed in some countries for similar reasons.[23] Euthanasia is decided by the team that takes care of the terminally ill patient, who has agreed to stop the treatment if it no longer makes any sense according to medical principles and experience and the ineffective available drugs and means. Pain that becomes refractory to analgesics, like strong drugs (cocaine, opium, etc) and no quality of life exists anymore. He is deeply depressed and disillusioned, resigned, indolent and ignorant of any joys and happiness in life. Sometimes the problems that arises are too difficult even for the doctors themselves.[24] The deep seated adherence of law (jurisprudence) to the intention, rather than the consequences themselves, is an important reference point in the moral assessment of any action.[25] In ethical discussions about euthanasia, the focus is often and exclusively on the involvement and responsibility of doctors, while the involvement of nurses is rarely given much attention. Although, euthanasia can be part of a medical end of life decision. Nurses are greatly involved in the issue. Nurses and technicians are the ones who are involved in the care of dying patients every day.[26] Abuses, arbitrary decision of the euthaniser, corruption in the form of bribery of the euthaniser (deprived of ethics), by relatives,

CONTENT

who want to get possession of a rich inheritance as soon as possible and dying only burdens them, supposedly.[27] Voluntary consent was included in the Patient's Rights Act. Consent is signed not only by those referring to euthanasia, but by all patients who consent, for example, to a surgical procedure or other operation, a more risky treatment. The purpose of the consent is to insure the medical staff and the institution against involuntary liability and possible lawsuits.[28, 29]

Cloning is also one of the ways of extending one's genes into eternity, only the person is not a product of biology only, but also of all external factors. Pedagogical, sociological circumstances and influencing factors. So, for example, the cloned old genius Einstein could possibly never become a new Einstein.[30] The misuse of euthanasia as an excuse for the Holocaust was part of the Nazi policy of eugenics.[31]

Latent suicides agree with the death penalty and euthanasia so that they don't have to kill themselves, because that brings stigma.[32] Euthanasia does not, but suicide carries a stigma, which means shame in front of society and for the family. For mercy or other reasons, assisted suicide is in contrast to the former criminal, illegal murder, as well as the legal - death penalty. Abolished in many countries by publication due to the principle of jurisprudence.[33] Unrealistic expectations are common in artificial attempts to prolong the mostly unnecessary treatment of sick persons deprived of a social sense of the usefulness of living in many ways that prologue the previously mentioned processes of dying.[34] In addition to bioethical deontological, medical, etc attempts to preserve dignity, it is important to take into consideration the more realistic individual state of the dying, in order to identify areas of special importance and value for the mentioned contexts and narratives in procedures before euthanasia.[35] Determination of the objective state of affairs and the contemporary euthanasia situation is inevitable, in order to really help the dying, before euthanasia itself.[36] Patient aware of the inevitable end and his torments in pain and weakness, loss of reason, ability to live, wanted to participate in his death actively, with his own hand and even with the help of someone else's. If he was no longer able or he didn't have the will, courage and ability to do it. The idea of euthanasia developed early.

There are also economic, material causes of attempts to end life.[37] Attitudes why people support or do not support euthanasia cannot be reduced to certain principles or arguments, but maintain an integrated assessment of a series of considerations, based on personal priorities and experiences.[38] Some countries of the European Union; Belgium and the Netherlands legalised euthanasia in 2002 and until recently were the only countries in Europe.[39] We live fast in a modern society, where technology and medicine are advancing every day offers more and more hope to seriously ill patients and the majority of society believes that euthanasia should not be legalised yet. Euthanasia is the subject and topic of many studies and philosophies. The attitude towards death changes in different cultures and historical periods. Man could never be indifferent, come to terms with his disappearance from the face of the Earth into nothingness.[40] The financial and economic aspects of euthanasia should not be ignored either, although in advanced countries (such as Switzerland and the Netherlands) the execution of euthanasia is expensive and the applicants are mostly wealthy clients.[41]

Conclusion

Different views exist concerning euthanasia, making it challenging to create a global team of professionals in the near future. Legalisation of euthanasia exists in some countries, while ethical and religious principles may limit it in most other countries. Although living in a modern society, legalising euthanasia raises many doubts and creates more questions than answers. One of the dilemmas is, for example, the criteria for candidates for voluntary euthanasia. Apart from their wishes, expressed in writing, publicly and officially, it's about their mental health and the ability for that act.

We believe in the premise that human life is of great value and should be loved and protected. We accept that individuals have the right to decide what doctors will or will not do. But the question is, is this right absolute or is it a question of the limits of autonomy. Scientists approach death rationally, yet the existence of certain positive effects leaves a lot of room for some future theoretical developments.

Ethics

Ethical approval was not sought for the present study because this publication was not a result of any primary clinical studies involving human subjects.

Acknowledgement

None.

Conflicts of interest

The authors declare that there is no conflict of interest.

Funding

The research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Data access

The data that support the findings of this study are available from the corresponding author upon reasonable individual request.

Author ORCID numbers

Alen Greš (AG):
0009-0003-7189-9340
Dijana Staver (DS):
0009-0000-5408-8915
Ljubomir Radovančević (LJR):
0000-0001-9039-2949

Author contributions

Conceptualisation: AG
Methodology: AG
Validation: LJR
Investigation: DS, LJR
Writing - original draft: AG, DS
Supervision: DS, LJR

References

1. Greš A, Staver D, Šakić B, Radovančević Lj. Thanatological perspectives in geriatrics and gerontopsychiatry. Scr Med. 2023;54(3):297-99. doi: 10.5937/scriptamed54-45477.
2. Germán Zurriaráin R. [Social Aspects of Euthanasia]. Cuad Bioet. 2019 Jan-Apr;30(98):23-34. Spanish. PMID: 30742451.
3. Snyder Sulmasy L, Mueller PS; Ethics, professionalism and human rights committee of the American college of physicians. Ethics and the legalization of physician-assisted suicide: an American College of Physicians Position Paper. Ann Intern Med. 2017 Oct 17;167(8):576-8. doi: 10.7326/M17-0938.
4. Živković MV, Pavlović ZS. [Euthanasia - legal aspect]. Vojno delo. 2019;71:73-81. Serbian. doi: 10.5937/vojdelo1906073Z.
5. Campbell CS. Mortal responsibilities: bioethics and medical-assisted dying. Yale J Biol Med. 2019 Dec 20;92(4):733-9. PMID: 31866788.
6. Cabrera T, Gabriela P, Coronel R, Alexix A, Cano M, Christina I. Perspective on assisted suicide and euthanasia: systematic review. AVFT. 2021;40:581-6. doi: 10.5281/zenodo.5557132.
7. Mastro C, Mason A, Susan E. Ethical issues and attitudes towards euthanasia. Mod Psychol Stud. 2017;22:28-36.
8. Brassington I. What passive euthanasia is. BMC Med Ethics. 2020 May 14;21(1):41. doi: 10.1186/s12910-020-00481-7.
9. Richardson S. An international expansion in voluntary euthanasia/assisted dying: The implications for nursing. Int Nurs Rev. 2023 Mar;70(1):117-26. doi: 10.1111/inr.12807.
10. Beaudry JS. Death as "benefit" in the context of non-voluntary euthanasia. Theor Med Bioeth. 2022 Dec;43(5-6):329-54. doi: 10.1007/s11017-022-09597-w.
11. Alcaraz-Britez AG. Dysthanasia, a problem for the medical staff. Rev Cienc Salud. 2022;4(2):108-11. doi: 10.53732/rccsalud/04.02.2022.108.
12. Karumathil AA, Tripathi R. Culture and attitudes towards euthanasia: an integrative review. Omega (Westport). 2022 Dec;86(2):688-720. doi: 10.1177/0030222820984655.

CONTENT

13. Picón-Jaimes YA, Lozada-Martinez ID, Orozco-Chinome JE, Montaña-Gómez LM, Bolaño-Romero MP, Moscote-Salazar LR, et al. Euthanasia and assisted suicide: An in-depth review of relevant historical aspects. Ann Med Surg (Lond). 2022 Feb 11;75:103380. doi: 10.1016/j.amsu.2022.103380.
14. Miller SM, Gallin S. An analysis of physician behaviors during the Holocaust: Modern day relevances. Conatus. 2019;4(2):265-85. doi: 10.12681/cjp.21147.
15. Ten Have H, Maria do Céu PN. Euthanasia, history. In: Dictionary of Global Bioethics. Cham, Germany: Springer International Publishing 2021;495. doi: 10.1007/978-3-030-54161-3.
16. Strand JJ, Kamdar MM, Carey EC. Top 10 things palliative care clinicians wished everyone knew about palliative care. Mayo Clin Proc. 2013 Aug;88(8):859-65. doi: 10.1016/j.mayocp.2013.05.020.
17. Swami M, Case AA. Effective palliative care: what is involved? Oncology (Williston Park). 2018 Apr 15;32(4):180-4. PMID: 29684230.
18. Chan KS. Palliative care: the need of the modern era. Hong Kong Med J. 2018;24(4):391-99. doi: 10.12809/hkmj187310.
19. Ivan Pavao II. Evangelium vitae. [Encyclical on the value and inviolability of human life]. Zagreb: Kršćanska sadašnjost 2003;66. Croatian.
20. Soares ME, Teixeira A, Tavares P. Shaping individual paths for decision-making: a fuzzy set approach of religious and humanistic beliefs leading to the (non) acceptance of euthanasia. Int J Organ Anal. 2023. doi: 10.1108/IJOA-12-2022-3522.
21. Abakare CO. Legal, social and ethical issues in euthanasia. J Soc Cult. 2021;(2):229-40. doi: https://doi.org/10.26858/prd.v1i2.19535.
22. Bekmurodova G. Concepts of social destruction philosophical analysis. IJIE. 2022;5(6):608-13. doi: 10.17605/ijie.v5i6.3325.
23. Radovančević Lj, Rakomić G. [Projection of the fear of death in cartoons on motives of suicide]. Ibidem. 1989:405-9. Croatian.
24. Poslon L. [Human dignity and the end of life]. Renewed Life. 2022;77(2), 235-48. Croatian. doi: 10.31337/oz.77.2.7.
25. Nedić T, Zibar L, Baraban B. [Terminological determination of the term euthanasia - legal, bioethical and medical-procedural implications]. Phil Inv. 2022;42(1):69-86. Croatian. doi: 10.21464/fi42104.
26. McEvoy P. Euthanasia, ethics, and the Gordian Knot: is the Hippocratic Code obsolete? Br J Gen Pract. 2015 Dec;65(641):624-5. doi: 10.3399/bjgp15X687721.
27. Ornek Buken N. Clinical ethical decision making process and determining factors at the end of life. Turkiye Klin J Med Ethics Law Hist-special Top. 2016;2(3):24-33.
28. López MP, Jima-González A. Analyzing the Spanish Euthanasia Law: Achievements and inconsistencies of the legal assistance to die. Revi Bioética y Derecho. 2023;147-64. doi: 10.1344/rbd2023.58.39990.
29. Mathieu-Nicot F, Chassagne A, Leboul D, Bousquet A, Trimaille H, Guirimand F, et al. Euthanasia and assisted suicide requests of end-of-life patients hospitalised in palliative care units: A qualitative wording analysis study. Med Palliat. 2023;22(3):119-26. doi: 10.21203/rs.2.18924/v1.
30. Segers S, Pennings G, Dondorp W, de Wert G, Mertes H. In vitro gametogenesis and reproductive cloning: Can we allow one while banning the other? Bioethics. 2019 Jan;33(1):68-75. doi: 10.1111/bioe.12505.
31. Stessman J, Paris B, Jacobs JM. Holocaust survivors: Health and longevity 70 years later. J Am Geriatr Soc. 2023 Oct;71(10):3199-207. doi: 10.1111/jgs.18485.
32. Radbruch L, Leget C, Bahr P, Müller-Busch C, Ellershaw J, de Conno F, et al; Board Members of EAPC. Euthanasia and physician-assisted suicide: A white paper from the European Association for Palliative Care. Palliat Med. 2016 Feb;30(2):104-16. doi: 10.1177/0269216315616524.
33. Dewi DAR, Haryono WS, Israhadi EI. Regulations for implementing passive euthanasia in the terminal stage patients (end of life) which is in accordance with justice and legal certainty in Indonesia. J Univ Stud. 2023;3(1):50-66. doi: 10.59188/eduvest.v3i1.717.
34. Westphal ER, Nowak WS, Krenchinski CV. Of philosophy, ethics and moral about euthanasia: the discomfort between modernity and postmodernity Clin Med Rev Case Rep. 2019;6:270. doi: 10.23937/2378-3656/1410270.
35. Ćurković M, Borovečki A. The bridge between bioethics and medical practice: medical professionalism. 1st ed. London, GB: Springer Nature 2022.
36. Scopetti M, Morena D, Padovano M, Manetti F, Di Fazio N, Delogu G, et al. Assisted suicide and euthanasia in mental disorders: ethical positions in the debate between proportionality, dignity, and the right to die. Healthcare (Basel). 2023 May 18;11(10):1470. doi: 10.3390/healthcare11101470.
37. Barsan MM, Dragu G. Euthanasia and assisted suicide. Pros and cons regarding the right to end your life with dignity. Bull Transilvania Univ Braşov. Series VII: Social Sciences Law. 2022;63-8. doi: 10.31926/but.ssl.2022.15.64.1.
38. Harris J. The survival lottery. In: Shafer-Landau R, ed. The ethical life: fundamental readings in ethics and moral problems. Oxfordshire, England: Oxford University Press, 2018; pp. 258-66.
39. Velasco Sanz TR, Pinto Pastor P, Moreno-Milán B, Mower Hanlon LF, Herreros B. Spanish regulation of euthanasia and physician-assisted suicide. J Med Ethics. 2021 Jul 30:medethics-2021-107523. doi: 10.1136/medethics-2021-107523.
40. Radovančević Lj. [Synergism of medicine and ethics]. Medicinski vjesnik. 1970;5:439-46. Croatian.
41. Krüger JM. Comparing the decriminalisation of assisted dying in Europe. Eur J Health Law. 2022 Oct 26;30(3):243-71. doi: 10.1163/15718093-bja10101.

CONTENT

Lagiou et al. Scr Med. 2024 Mar-Apr;55(2):251-6. DOI:10.5937/scriptamed55-47669
HISTORY OF MEDICINE

Ocular and Eyelid Surgical Anatomy in Georg Bartisch's "Ophthalmodouleia"

Efstathia Lagiou,[1] Konstantinos Laios,[2] Gregory Tsoucalas,[1] Ioannis Zaganas,[3] Efstathios T Detorakis,[4] Marianna Karamanou[2]

Abstract

Georg Bartisch, a 16th century barber surgeon, published in 1583 his treatise entitled "Ophthalmodouleia" (Greek term meaning eye service), a work in German to promote ophthalmology for his countrymen barber surgeons. He did not have an academic education nor knew classical languages, he had used a triplet in terminology by using German, Hellenic and Latin nomination in his anatomical descriptions. Various accurate illustrations and a peculiar system of presentation with flap to liken an in-depth presentation were demonstrated to add prestige in his work. This raises concerns for another medical surgeon to have helped for this publication. Bartisch innovative approaches introduced various surgical tools. Cataract surgery was the epitome of his work. Anatomy of both the eye and the eyelids was there for only to serve the operation. Religion, magic and Galenic views presented barriers for Bartisch's scientific development. However, he is considered as the patron of German School of Ophthalmology.

Key words: Galen; Cataract; Eyelid cutters; Dissected plates; German ophthalmology.

1. Department of History of Medicine and Medical Deontology, Medical School, University of Crete, Greece.
2. Department of History of Medicine and Medical Ethics, Medical School, National and Kapodistrian University of Athens, Athens, Greece.
3. Department of Neurology, Medical School, University of Crete, Crete, Greece.
4. Department of Ophthalmology, Medical School, University of Crete, Crete, Greece.

Citation:
Lagiou E, Laios K, Tsoucalas G, Zaganas I, Detorakis ET, Karamanou M. Ocular and eyelid surgical anatomy in Georg Bartisch's "Ophthalmodouleia". Scr Med. 2024 Mar-Apr;55(2):251-6.

Corresponding author:
KONSTANTINOS LAIOS
E: konstlaios@gmail.com

Received: 12 November 2023
Accepted: 19 December 2023

Introduction

Georg Bartisch (1535-1607) is projected as the founder of Ophthalmology in Germany (Figure 1a). Although he had not received an academic medical education and belonged to the circle of the barber surgeons his accomplishments in ocular surgery secured him a place in history. He had begun his apprenticeship since the age of 13 gradually developing amazing skills in ophthalmology, being considered as a pioneer in this field. In 1588, he became the official oculist of Duke Augustus I of Saxony (1526-1586).[1] During his medical career Bartisch wrote two important treatises. The first, published in 1575 about lithotomies under the title "Art book in it is the whole thoroughly right definite report and proof and instruction about hard painful tearing pain embarrassing bladder stones" (Original German title: *Kunstbuch derinnen ist der gantze gründlich volkommene rechte gewisse bericht und erweisung unnd Lehr des Hartenn Reissenden Schmertz hafftigenn Peinlichen Blasenn Steines*) had not received a great acceptance by the medical cast.[2] The second one though, a book about eye diseases and ocular surgery gained inordinate fame. Titled "Ophthalmodouleia, this is eye-service: newer and successive report of causes and findings of all afflictions and defects of eyes and face" (Original German title: *ΟΦΘΑΛΜΟΔΟΥΛΕΙΑ, das ist Augendienst: newer und wolgegründter Bericht von ursachen vnd Erkenntnüs aller Gebrechen Schäden*

Copyright © 2024 Lagiou et al. This is an open access article distributed under the Creative Commons Attribution License (CC BY), which permits unrestricted use, distribution and reproduction in any medium, provided the original work is properly cited.

CONTENT

und Mängel der Augen und des Gesichtes), published in 1583, it became the first ophthalmology book written in German (Figure 1b).[3]

Figure 1: The Barber Surgeon Georg Bartisch (1a) and his treatise ΟΦΘΑΛΜΟΔΟΥΛΕΙΑ (Ophthalmodouleia), Stöckel, Dreßden, 1583 (1b)

This historical vignette aimed through documentary research to review and present the majestic figure in ophthalmology Georg Bartisch, recording simultaneously his opinions in ocular and eyelid surgical anatomy.

Georg Bartisch's ocular and eyelid anatomy

In his fundamental work in ocular surgery the third chapter of the first part was devoted to the anatomy of the eye as a human organ. Both eyes were considered as extensions of the brain, being parts of the central nervous system. This explains an inner towards the outer parts of the eye anatomic description. He believed that the most important part of the eye was the ocular nerve. He had suggested that the optical nerve was being developed through the first inner ocular tunic named retina. He had proposed a horizontal almost oval nerve shape being extended beyond the centre of the organ anteriorly. He had supported the idea of various humours being included in the eye. Thus, retina was filled by *vitreous humour*, while crystal lens was filled by crystalloid. The small size of the *crystalloid humour* covered by the arachnoid tunic combined with its eccentric place was forming the concave shape of the anterior border of the retina. Outer of the retina and distantly reaching the uvea the exists the choroid tunic. It seems that the later included the above-mentioned anatomical structures, while the rest of the space remained was filled with the *aqueous humour*. Bartisch gave vivid descriptions of the pupil, cornea, sclera and conjunctiva. Cornea covered uvea, outer was sclera which was considered as an extension of the *dura mater* and conjunctiva was the outer tunic of the eye which extended at the limits of the ocular muscles. Regarding the ocular muscles, he had described six oculomotor muscles, up, down, right and left of the bulbar, two others rising from the inner and the outer canthus (noted by Bartisch as big and small canthus) and finally the *musculus retractorius bulbi* which encircled the ocular nerve.[3]

Bartisch considered the eyelids as the entity which fortify the eyes. Each eyelid was attached to the nose through the large canthus and through the small one to the cheekbone. The movement of the upper eyelids (only those were considered as movable parts) was mentioned as a wonderful property of the human body. Thus, the upper eyelids were structures being moved by muscles which arose locally, reaching the tarsus of the eyelids, at points just below their skin fold. Their innervation was recorded as being shared with that of the temporalis muscles and that of the occipital and forehead regions. Tarsus was mentioned and the ligament-cartilage under the skin part which gave shape to the eye.[3]

The first thing which is worthwhile to note that although Bartisch's book was written in German, he used the Latin names for every anatomical part of the eye, while sometimes he had also added the Hellenic terms. He had recorded the following terms, nervus opticus, retina or *retiformis* or *ἀμφιβληστροειδής* (Greek), *humour vitreous* or *vitriformis* or glacialis or *ὑαλοειδής* (Greek), *humour crystallinus*, *humour albugineus* or *aqueous* or *ὑδατοειδής* (Greek), *aranea* or *ciliaris* or *ἀραχνοειδής* (Greek), *pia mater* or *tenuis membranea* or *secundina* or *χοροειδής* (Greek), *uvea* or *acinosa* or *corona* or *στεφάνη* (Greek) or *ἴρις* (Greek) or *πανοειδής* (Greek), *cornea* or *κερατοειδής* (Greek), *dura mater* or *dura* or *crassa membrana* or *sclerotica* or *σκληρός* (Greek), *conjunctiva* or *adnata* or *ἐπιπεφυκότας* (Greek), *musculis* (for ocular muscles).[3]

The second to note is that Bartisch drawn his own-coloured anatomical sketches using flaps,

CONTENT

as successive sheets one above the other in order for the reader to acquire an in-depth perception. By lifting the upper flap to see the subjacent anatomical parts, reaching inner layers, tunics and humours of the eye would have been depicted in a profile mode. Although he had drawn some of the ocular veins, he did not thoroughly describe them in his ocular anatomy. The same happened for the arteries too, which had been almost neglected.[3]

Discussion on surgical anatomy and era's achievements

Bartisch lack of higher medical education was replaced by superstition and the divine combined with knowledge of the past. Both parents of the oculist surgeon should have been God-fearing, the surgeon himself should have been ambidextrous so that he could easier operate and prayers should have been used to attract God's help and remove magic. Magic was among the causes of various diseases and surgeon should have been married to dispel it. Bartisch worshiped God and Galen. The Galenic views on anatomy dominated his thought. Nevertheless, he had suggested that the optical nerve was the epicentre of this sense organ, being a projection of the brain. *Ophthalmodouleia* was the first ophthalmology textbook written for the common German people, with the purpose to educate barber surgeon of the time.[4]

Bartisch considered eyelids as the structures which protect the eye, which in its turn originates from the central nervous system. This is why he had also described the anatomy of the brain in an ocular manuscript to emphasise upon their tissue connection. To testify his opinions, he had added various anatomical sketches depicting from the top of the head an open cranium to demonstrate the brain as seen from above going deeper until the area of the optic nerves. The optic chiasm was an already known anatomy fact since the antiquity,[5] recorded by Rufus of Ephesus (1st c AD)[6] and Galen (2nd c AD),[7] (Arrington and Mart-Ibanez, 1959) while Leonardo di ser Piero da Vinci (1452-1519)[8] and Andreas Vesalius (1514-1564)[9] had already illustrated it in their anatomical drawings. Nevertheless, Bartisch failed to depict it and the optical nerves were simply represented as thin straw lines which almost form an oblique angle when they reach the inner parts of the brain.[3]

Bartisch had unambiguously stated that he did not received an academic medical education. Therefore, his anatomy knowledge especially for the eye was probably derived from his practical experience. As it was almost impossible to have dissected an eye, he had most probably performed dissections in animal eyes. Being a practical physician he was not interested in a detailed and accurate description of anatomy. However, his work contained excellent anatomical figures, presented in a peculiar way. The plates depicting the dissected eye, were presented as "dissected plates" as they were named. Layers of flaps demonstrated topographical anatomy giving the impression and an imaginable human body (Figure 2).[10]

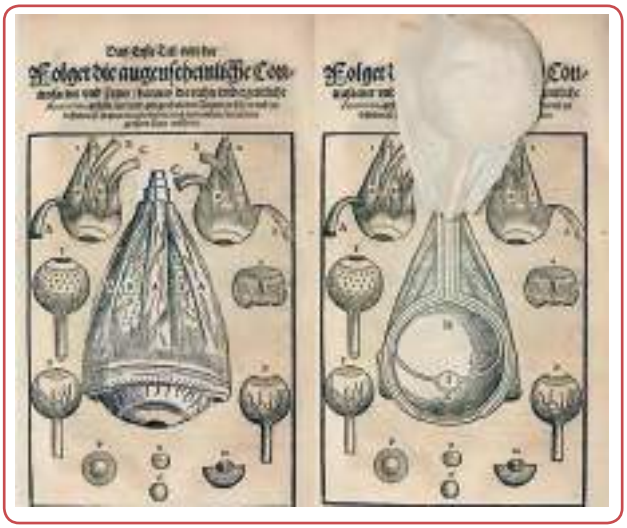


Figure 2: Bartisch's anatomical sketches of the eye using the flap-dissected plates system of presentation, figures derive from his book Ophthalmodouleia

Ocular anatomy by Bartisch[11] was influenced by Andreas Vesalius' anatomy book[12] published a few years earlier, filtered by Galen's relevant anatomical theories, even though the contradiction that Vesalius fought Galenic views.[13] The similarities between Vesalius and Bartisch such as the oculomotor muscles, *musculus retractorius bulbi* and the descriptions of ocular tunics and humours were obvious, but an exact copy can't be supported. Bartisch failed to describe the seventh muscle enveloping the optical nerve, but he had surprisingly displayed excellent drawings of the six muscles, which were better than those included in Vesalius work.[14] His volition to use Latin and Greek terms for

CONTENT

the anatomical parts and the use of flaps was probably an attempt to give a more sophisticated approach for his treatise. Bartisch himself was ignorant of the classical languages; the Greek and Latin phrases with which his book is larded were probably contributed by some itinerant scholar or perhaps an educated surgeon to allow him to produce an appreciable self-published treatise.[15]

Apart from surveying the descriptive anatomy of the eye, it is of importance to examine the surgical anatomy of the eye in Bartisch's work, so that to confirm the minor role that anatomy had played in his daily practice. One third of his treatise was devoted to the surgical treatment of various ocular diseases, while many drawings depicted patients and the practice of ocular operations upon them. Meanwhile various surgical tools and apparatuses were also demonstrated.[3] Thus, surgical operations, as those of cataract and tumour excisions attracted attention. Regarding cataract surgery which was the commonest in the era[16] (Heinrich, 1916), he had been performing it by using the couching method. Although Antyllos (1st half of 2nd c AD)[17] and Abu'l-Qûsim Ammar ibn Ali al-Mawsili (9th - 10th c AD)[18] had introduced the suction method, Bartisch was among the pioneers who followed the couching method. He was capable to introduce a fine needle temporally from cornea to conjunctiva, then by turning it forward, he could reach the crystal lens, pushing it downwards. He had underlined how dangerous this operation was, by mentioning a cluster of symptoms like massive haemorrhage, severe pain, oedema, tearing and photophobia.[3] It appears that anatomy was only respected for operation to be as successful as it could be and had not been taken into account its complexity. Anatomy existed in such an extent to only help ocular surgeon to reach crystal lens. As expected, Bartisch's daily experience allowed him to perform the operation by pushing crystal lens or humour crystallinus anteriorly, deeper than those who previously attempted it. The cataract operation was the main applied in eyeball and orbit, while the removal of foreign bodies from the white substance was also performed. Another type of surgical intervention concerned pterygium, trichiasis, eyelid tumours and ptosis,

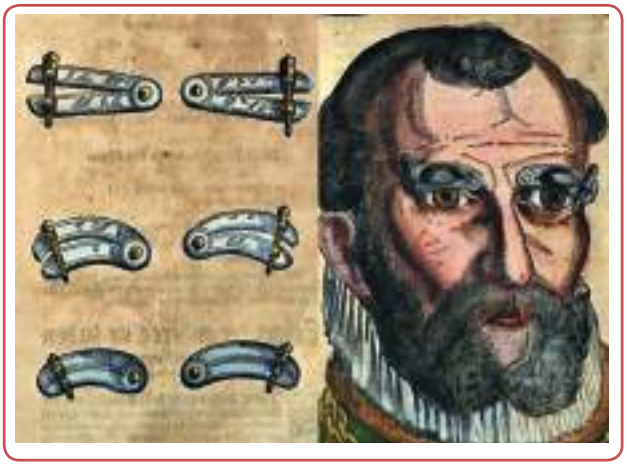


Figure 3: Eyelid cutters (left) and its application for the excision of tumorous formations of the eyelids (right) from inside Bartisch's book Ophthalmodouleia

all treated with excision of an eyelid fold. The technique was simple, cut and remove, scalpel, cutters and innovative tools, almost as if he did not care about patient's pain or aesthetic results (Figure 3). *Lagophthalmos* was not mentioned.[3] The brutality of Bartisch surgical methods may found in almost all of his approaches. From the enucleation of eyeball and exenteration of the anatomical parts of the orbit, all exhibited rough manipulations.[19] Bulbar and orbital cancer or severe injuries in those anatomical areas or acute inflammation misinterpreted as cancer, were performed by cutting the inflicted area, considered as malignancies. A series of novel surgical instruments in deferent sized according the dimensions of the patient's eyes, clumsy in appearance had been introduced due his innovative imagination. During the enucleation, surgeon could pass a suture vertically through the eyeball and then pull it out by lifting the upper eyelid and pushing a special spoon-like scalpel towards the bone and sclera. For his exenteration operation he used all his "violent" tool like chisels, scrapers and knives in order just to remove all tissue parts until the exposure of the optical nerve.[3] Muscles and bone structures were not to be saved and had been sporadically injured. Therefore, these techniques were later improved by majestic figures in ocular surgery, like Wilhelm Fabricius von Hilden (1560-1634)[20] and Carl Ferdinand Ritter von Arlt (1812-1887).[21]

CONTENT

Conclusion

Georg Bartisch was an ophthalmologist who in 1583 published a monumental inclusive text in German devoted exclusively to the eye. The grandiose language, including Greek and Latin create suspicion that Bartisch employed a scribe to edit and embellish the book for him. Galenic limitations and absence of medical knowledge restricted somehow surgical methods described in *Ophthalmodouleia*. This treatise offered nothing in the study of descriptive ocular anatomy as it followed previous knowledge. Empirical barber surgeon, manufacturer of peculiar tools, good writer, Bartisch became famous for his cataract surgical method. Meanwhile, his beautiful illustration and presentation techniques still remain somehow in vogue; a fact which alone testifies a scientific magnitude. Unexpectedly, Georg Bartisch has a place among the most significant figures in ophthalmology, coined to be the founder of the German school.

Ethics

Our institution does not require ethics approval for articles reporting the history of medicine.

Acknowledgement

None.

Conflicts of interest

The authors declare that there is no conflict of interest.

Funding

The research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Data access

The data that support the findings of this study are available from the corresponding author upon reasonable individual request.

Author ORCID numbers

Efstathia Lagiou (EL):
0000-0002-7664-2662
Konstantinos Laios (KL):
0000-0002-4746-0843
Gregory Tsoucalas (GT):
0000-0002-2595-9686
Ioannis Zaganas (IZ):
0000-0002-0774-5772
Efstathios T Detorakis (ETD):
0000-0003-1251-3965
Marianna Karamanou (MK):
0000-0002-1307-7707

Author contributions

Conceptualisation: EL
Methodology: EL, KL, GT
Investigation: EL, KL, GT
Writing - original draft: EL, KL
Writing - review and editing: GT, IZ, ETD, MK
Supervision: GT, IZ, ETD, MK

References

1. Eckart WU, Gradmann C. Ärtze Lexikon von der Antike biz zu Gegenwart. Heidelberg: Springer Medizin Verlag; 2006. German. doi: 10.1007/978-3-540-29585-3.
2. Bartisch G, Mankiewicz. Kunstbuch derinnen ist der gantze gruendliche volkommene rechte gewisse Bericht und Erweisung unnd Lehr des hartenn reissenden Schmertz hafftigenn peinlichen Blasenn Steines: 1575. Berlin: O. Coblentz; 1905. German.
3. Bartisch G. Ophthalmodouleia. Das ist Augendienst. Newer und wolgegründter Bericht von ursachen und erkenntnüs aller Gebrechen Schäden und Mängel der Augen und des Gesichtes wie man solchen anfenglich mit gebürlichen Mitteln begegenen vorkom. Dreßden: Stöckel; 1583. German.
4. Spalding JA. Ophthalmology ancient and modern. Transactions of the Maine Medical Association 1882;7:250-74.

CONTENT

5. Costea CF, Turliuc Ş, Buzdugă C, Cucu AI, Dumitrescu GF, Sava A, et al. The history of optic chiasm from antiquity to the twentieth century. Childs Nerv Syst. 2017 Nov;33(11):1889-98. doi: 10.1007/s00381-017-3564-1.
6. Daremberg C, Ruelle CI. De corporis humani appellationibus. Oeuvres de Rufus d'Éphèse. Paris: Imprimerie Nationale; 1879. French.
7. Arrington GE Jr, Mart-Ibanez F. A history of ophthalmology. New York: MD Publications; 1959.
8. O'Malley CD. Sounders JB, Sounders CM, da Vinci L. Leonardo da Vinci on the human body: the anatomical, physiological, and embryological drawings of Leonardo da Vinci. With translations, emendations and a biographical introduction. New York: Henry Schuman; 1952.
9. De Laey JJ. The eye of Vesalius. Acta Ophthalmol. 2011 May;89(3):293-300. doi: 10.1111/j.1755-3768.2009.01679.x.
10. Alexander JR. Dissected plates. Montreal: McGill University Publications Library: 1921.
11. Magnus H. Historische Tafeln zur Anatomie des Auges: ein Beitrag zur Geschichte der anatomischen Abbildungen des Auges. Rostock: Stiller'sche Hof- und Universitätsbuchhandlung; 1877. German.
12. Vesalius A. Andreae Vesalii Bruxellensis De humani corporis fabrica libri septem. Basileæ: Ex officina Ioannis Oporini; 1543. Latin.
13. Hirschberg J. Geschichte der Augenheilkunde. Band I-II. Leipzig: Engelmann; 1899-1918. German.
14. Lowe RF. Georg Bartisch: Ophthalmodouleia, der Augendienst, 1583. A treatise on service of the eyes and a review of the chapter on strabismus. Aust N Z J Ophthalmol. 1997 Nov;25(4):295-8. doi: 10.1111/j.1442-9071.1997.tb01518.x.
15. Hook DH, Norman J. The Haskell F. Norman library of science and medicine. San Francisco: J. Norman; 1991.
16. Heinrich C. Die Lehre vom Star bei Georg Bartisch (1535-1606). Jena: G. Fischer; 1916. German.
17. Leven KH. Antike Medizin. Ein Lexikon. München: Beck; 2004. German.
18. Laios K, Moschos MM, George A. Ammar ibn Ali al-Mawsili and His innovating suction method for the treatment of cataract. Surg Innov. 2016 Aug;23(4):433. doi: 10.1177/1553350615618289.
19. Wood CA. A system of ophthalmic therapeutics; being a complete work on the non-operative treatment, including the prophylaxis, of diseases of the eye. Chicago, IL: Cleveland Press; 1909.
20. Fabricius Von Hilden W. Guilielmi Fabricii Hildani Paterniacensis chirurgi ordinarii Observationum et curationum chirurgicarum centuriae. Wustii Jun., Francofurti ad Moenum: Typis ac sumptibus B.C. 1682. Latin.
21. Arlt CFR von. Operationslehre. Handbuch der gesamten Augenheilkunde. Bd.III.1. Engelmann; 1874. German.

CONTENT

Ravishankar and Sunil. Scr Med. 2024 Mar-Apr;55(2):257-61. DOI:10.5937/scriptamed55-48547

PROFESSIONAL ARTICLE

Computed Tomography Imaging Characteristics of Neck Paragangliomas: A Retrospective Analysis

Dev Ravishankar,[1] Devika Sunil[2]

Abstract

Background/Aim: Paragangliomas are rare neuroendocrine tumours arising from paraganglia of the autonomic nervous system. Computed tomography (CT) imaging plays a crucial role in the evaluation and characterisation of neck paragangliomas. This retrospective study aimed to analyse the CT imaging features of neck paragangliomas to enhance diagnostic accuracy and delineate the radiological characteristics associated with these tumours.

Methods: A retrospective review of CT imaging studies of patients diagnosed with neck paragangliomas from March 2021 to October 2023 was conducted. Imaging characteristics including tumour location, size, enhancement pattern, vascularity, calcifications, adjacent tissue involvement and relationship with surrounding structures were analysed.

Results: A total of 87 patients with histologically confirmed neck paragangliomas were included in the study. CT imaging revealed typical findings of neck paragangliomas ie well-defined hyper-vascular masses with avid contrast enhancement, commonly located at the carotid bifurcation or along the carotid sheath. In addition, characteristic flow voids and the presence of feeding vessels were observed on CT angiography in a significant number of cases. The imaging analysis also identified calcifications and encasement of adjacent structures as frequent features of advanced-stage paragangliomas.

Conclusions: CT imaging of neck paragangliomas demonstrated consistent radiological features, including hypervascularity, contrast enhancement and distinct anatomic locations. Knowledge of these imaging characteristics is essential for accurate diagnosis and preoperative planning. Recognition of these features on CT imaging can aid in differentiating paragangliomas from other neck masses and facilitate appropriate management strategies.

Key words: Neck paraganglioma; Computed tomography; Diagnostic imaging; Hypervascularity.

1. Department of Radiodiagnosis, Sree Uthradom Thirunal Academy of Medical Science (SUTAMS), Trivandrum, India.
2. Department of Oncology, Sree Gokulam Medical College and Research Foundation (SGMCRF), Trivandrum, India.

Citation:
Ravishankar and Sunil. Computed tomography imaging characteristics of neck paragangliomas: a retrospective analysis. Scr Med. 2024 Mar-Apr;55(2):257-61.

Corresponding author:
DEVIKA SUNIL
E: devikadev91011@gmail.com
E: devravis@gmail.com

Received: 4 January 2024
Revision received: 19 March 2024
Accepted: 19 March 2024

Introduction

Paragangliomas are rare neuroendocrine tumours arising from the paraganglionic tissue of the autonomic nervous system, with the potential to develop in various anatomical locations. Approximately 3-5 % occur in the head and neck region.[1] Among head and neck paragangliomas, those located in the neck present specific diagnostic and management challenges due to their proximity to critical structures such as major blood vessels and cranial nerves. Within the neck,

Copyright © 2024 Ravishankar and Sunil. This is an open access article distributed under the Creative Commons Attribution License (CC BY), which permits unrestricted use, distribution and reproduction in any medium, provided the original work is properly cited.

CONTENT

paragangliomas more commonly arise from the carotid body, vagus nerve and jugular paraganglia.[2]

Computed tomography (CT) especially contrast enhanced computed tomography (CECT) plays a crucial role in the evaluation of neck paragangliomas, not only providing detailed anatomical and functional information but offer additional insights into tumour characteristics and vascular involvement. Accurate diagnosis and characterisation of neck paragangliomas are essential for guiding appropriate management strategies, including surgical resection, embolisation and radiation therapy. CT imaging plays a pivotal role in the assessment of neck paragangliomas, providing detailed anatomical information and characterisation of these tumours.[3-6] However, the specific diagnostic imaging features of neck paragangliomas on CT which is essential for optimising the diagnostic and management strategies have not been comprehensively documented in available literature. By identifying consistent imaging findings, this study seeks to contribute to improved recognition and management of neck paragangliomas.

This retrospective study aimed to analyse the CT imaging characteristics of neck paragangliomas to enhance diagnostic accuracy and delineate the radiological features associated with these tumours.

Methods

A retrospective review of patients diagnosed with neck paragangliomas at Post Graduate Medical Institute (Sree Uthradom Thirunal Academy of Medical Sciences (SUTAMS), Thiruvananthapuram, India) from March 2021 to October 2023 was conducted. The study was authorised by Institutional Ethics Committee (IEC) of SUTAMS and informed written consent from all patients were taken before their participation.

Inclusion criteria were patients ranging in 18 to 80 years age group with slowly growing palpable neck masses who underwent CT evaluation. Patients with fever and having painful, inflammatory neck masses were not included in the study.

Multidetector CT (MDCT) examination was performed using 16-slice *Revolution CT scanner* (GE Medical Systems) and entire neck from petrous superior border to thoracic inlet was scanned craniocaudally within 10-15 s. CT angiography (CTA) was done for all patients using a *Medrad* pressure injector for pushing 80 mL non-ionic water-soluble contrast through a 18 G cannula into the antecubital vein at a flow rate of 4 mL/s. CT acquisition parameters were 120 kVp, 440 mAs, pitch of 1.375:1 at 1.25 mm slice thickness and 0.625 mm recon interval with a large FOV.

Evaluation for key CT features like location, degree of vascularisation, contrast enhancement features and presence of feeding arteries was conducted and findings were documented. CT findings were later correlated with histopathology / culture reports.

For statistical analysis the data observed were recorded and analysed using International Business Machines (IBM) Statistical Package for the Social Sciences (SPSS) version 20.0 software for Windows. Statistical significance was tested by Fisher's exact test. P-value < 0.05 was taken as significant.

Results

The CT imaging analysis of 87 patients satisfying the inclusion criteria showed hypervascularity and rapid wash in and wash out of contrast in all patients and arterial feeding vessels supplying the paragangliomas could be demonstrated in 80 patients (92 %) (Table 1). Paragangliomas including glomus (n = 37, 42 %) and carotid body tumours (n = 50, 57 %) were the commonest lesions.

Table 1: Computed tomography (CT) characteristics of paraganglioma

CT characteristics of paraganglioma	Yes n (%)	No n (%)	p-value*
Avid contrast enhancement/ hypervascularity	87 (100 %)	0 (0 %)	< 0.001
Feeding vessel	80 (92 %)	7 (8 %)	< 0.005
Rapid wash-in and wash-out	87 (100 %)	0 (0 %)	< 0.001

**Fisher's-exact test;*

Statistical analysis of CT study data revealed a significant correlation ($p < 0.05$) between hypervascularity, key contrast enhancement features and presence of feeding artery thereby establishing CT as a one shop stop for evaluation of neck

CONTENT

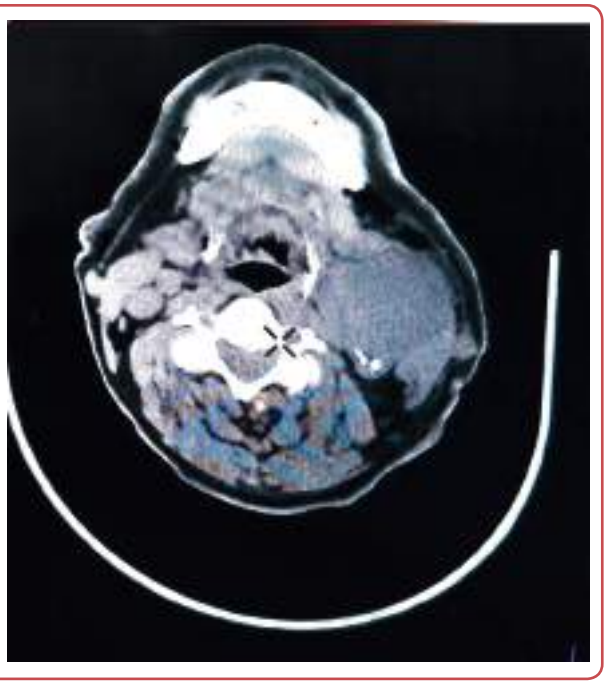


Figure 1: Plain computed tomography (CT) neck showing a soft tissue density lesion in the left anterior triangle region. No intralesional calcifications were seen.

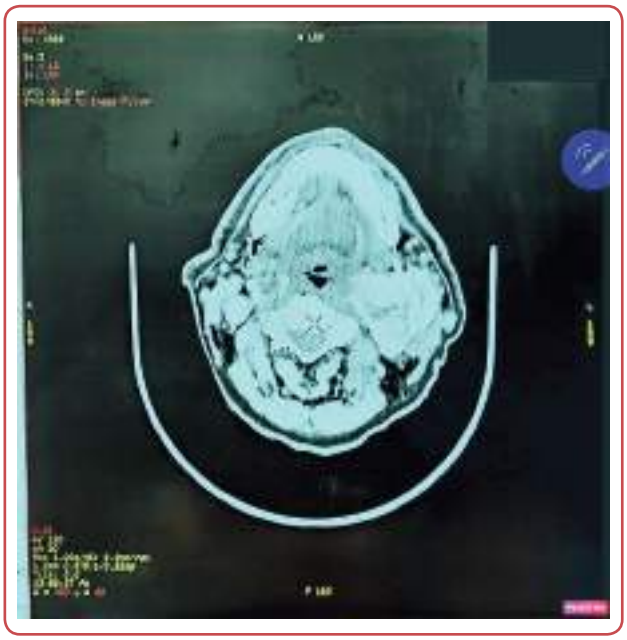


Figure 2: Contrast enhanced computed tomography (CECT) neck demonstrates a well-defined avidly enhancing soft tissue mass at the carotid bifurcation with characteristic splaying of the internal carotid artery and external carotid artery. No evidence of adjacent infiltrative or inflammatory changes was seen.

paragangliomas negating the need for any other modality including magnetic resonance imaging (MRI). CT capabilities make it clear choice over MRA in identifying arterial feeders of paragangliomas due to its wider clinical accessibility and better patient tolerance profile (Figure 1 and 2).

Discussion

In presented study, paragangliomas including glomus (n = 37, 42 %) and carotid body tumours (n = 50, 57 %) were the commonest lesions which agreed with the study of Whalen RK et al[7] which stated that 80 % of extra-adrenal paragangliomas are either carotid body or glomus tumours. Study was concordant with Van den Berg et al[5] report in 2005 about the various CT imaging findings specific to common neck paragangliomas but their study was not a dedicated study in this topic while presented study was a retrospective study conducted with a good number of clinical cases. Boedeker et al[8] in 2004 published their experience in diagnostic ultrasound, CT and MRI evaluation of head and neck paragangliomas but as well with a limited number of cases.

Most of the literature on this topic was before 2010 and also was not specifically to do with common neck paragangliomas nor was it conducted as a retrospective study with a statistically significant number of patients. To authors' knowledge no recent studies on this important topic of imaging of neck paragangliomas were published in any journal of note. Hence this being a recently conducted study incorporates current demographics, imaging technology and data.

The comprehensive analysis of CT data in this study provides valuable insights into the imaging characteristics of neck paragangliomas. The observed correlations between specific CT features and clinical parameters highlight the potential of advanced imaging techniques in predicting clinical behaviour and guiding management decisions. The avid enhancement on contrast-enhanced CT images suggests a high vascularity of the tumours, which may have implications for preoperative embolisation and surgical planning. Vascular encasement or displacement when visualised on CECT can influence the choice of surgical approach and the risk of intraoperative bleeding or nerve injury. These findings underscore the importance of a multimodal imaging approach in the evaluation of neck paragangliomas and demonstrate the potential of CT in providing valuable prognostic information. CT imaging of neck paragangliomas demonstrates consistent radiological features including hypervascularity, contrast enhancement and distinct anatomic locations. Recognition of these imaging characteristics is crucial for accurate diagnosis and preoperative planning. The identification

CONTENT

of characteristic CT imaging features can aid in differentiating paragangliomas from other neck masses and guide appropriate treatment strategies. Familiarity with these imaging findings enhances the ability of radiologists and clinicians to recognise and characterise neck paragangliomas, ultimately contributing to improved patient care and treatment outcomes.

The only limitations of the study are the inherent contraindications of CT like allergy to iodine contrast, radiation risk and those patients with low e-GFR who could not be taken up for contrast CT studies.

Conclusion

This research article presents a comprehensive analysis of CT data on neck paraganglioma that offers valuable insights which aids in the radiological characterisation of neck paragangliomas and establishes CT imaging as a viable mean for accurate diagnosis with implications for therapeutic decision-making and potential for personalised treatment approaches in neck paragangliomas.

Ethics

All procedures performed in this study were in accordance with the ethical standards of the Institutional and / or National research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. The study was approved by Institutional Ethical Committee - SUTAMS IEC with approval No 49(3)/IEC/SUTAMS/2021, dated 1 March 2021.

Acknowledgement

The authors acknowledge the support of all colleagues and technical staff at SUTAMS and SGMC. We also thank all the patients who agreed to participate in our study.

Conflicts of interest

The authors declare that there is no conflict of interest.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Data access

The data that support the findings of this study are available from the Sree Uthradom Thirunal Academy of Medical Science (SUTAMS) patient registry after obtaining permission from Chief Administrative Officer (CAO) and Institutional Ethical committee clearance upon reasonable individual request.

Author ORCID numbers

Dev Ravishankar (DR):
0009-0008-2338-9334
Devika Sunil (DS):
0000-0002-5491-4428

Author contributions

Conceptualisation: DR
Methodology: DR
Software: DR, DS
Validation: DR
Formal analysis: DR
Investigation: DR
Resources: DR
Data curation: DR
Writing - original draft: DR, DS
Writing - review and editing: DR, DS
Visualisation: DR
Supervision: DR
Project administration: DR

CONTENT

References

1. Offergeld C, Brase C, Yaremchuk S, Mader I, Rischke HC, Gläsker S, et al. Head and neck paragangliomas: clinical and molecular genetic classification. Clinics (Sao Paulo). 2012;67 Suppl 1(Suppl 1):19-28. doi: 10.6061/clinics/2012(sup01)05.
2. Sandow L, Thawani R, Kim MS, Heinrich MC. Paraganglioma of the head and neck: a review. Endocr Pract. 2023 Feb 1;29(2):141-7. doi: 10.1016/j.eprac.2022.10.002.
3. Lin EP, Chin BB, Fishbein L, Moritani T, Montoya SP, Ellika S, et al. Head and neck paragangliomas: an update on the molecular classification, state-of-the-art imaging, and management recommendations. Radiol Imaging Cancer. 2022 May;4(3):e210088. doi: 10.1148/rycan.210088.
4. Thelen J, Bhatt AA. Multimodality imaging of paragangliomas of the head and neck. Insights Imaging. 2019 Mar 4;10(1):29. doi: 10.1186/s13244-019-0701-2.
5. Van Den Berg R. Imaging and management of head and neck paragangliomas. Eur Rad. 2005 Jul;15:1310-8. doi: 10.1007/s00330-005-2743-8.
6. Dhiman DS, Sharma YP, Sarin NK. US and CT in carotid body tumor. Indian J Radiol Imaging. 2000;10:39–40. doi: 10.7860/IJARS/2017/29448:2283.
7. Whalen RK, Althausen AF, Daniels GH. Extra-adrenal pheochromocytoma. J Urol. 1992 Jan 1;147(1):1-10. doi: 10.1016/s0022-5347(17)37119-7.
8. Boedeker CC, Ridder GJ, Schipper J. Paragangliomas of the head and neck: diagnosis and treatment. Fam Cancer. 2005;4(1):55-9. doi: 10.1007/s10689-004-2154-z.

CONTENT

Instructions to authors

Scripta Medica (Banja Luka) is a peer-reviewed, international open access journal published bimonthly. It is abstracted/indexed by EBSCO, Google Scholar, SCIndeks, Crossref, Index Copernicus International (ICI), Directory of Open Access Journals (DOAJ) and Scopus. All articles can be downloaded free of charge from the web site (http:// www.scriptamedica.com/en) under the license: the Creative Commons Attribution 4.0. International (CC BY 4.0) (https://creativecommons.org/licenses/ by/4.0/).

Scripta Medica publishes editorials, original articles, review articles, current topics, special articles, history of medicine articles, professional articles, case reports, images in clinical medicine, letters to the editor and *in memoriam* notes.
Scripta Medica publishes papers in English only that were not published before, nor submitted to any other journals, in the order determined by the Editor-in-Chief. Each submitted manuscript is checked by the plagiarism-detecting software *iThenticate*.

General instructions

1. Manuscripts should be submitted in the *doc or *docx format (Microsoft Word), using the Times New Roman font. The text should be single spaced in 12 point. The main heading should be 14 point **bold**. Subheadings should be 12 point **bold**. Tables must be in 10 point, single spaced; headings within tables should be in 10 point **bold**; the main table heading should be in 12 point **bold**; legends should be single spaced in 10 point. Figures should be made using standard graphic formats (*pdf, *ai, *cdr). Photographs should be delivered in *jpg format, 1:1, 300 dpi or higher resolution, as separate files.

2. Language. *Scripta Medica* uses the British spelling of the English orthography. For details please consult the University of Oxford Style Guide. American spelling should be limited to the official titles of the US institutions and original US references only.

3. Drugs and chemicals should be indicated by international non-proprietary names (INN) or generic names. Instruments, apparatus or other devices should be indicated by trade names, with the producer's name and place of production indicated in brackets.

4. Numbers in text and tables should be provided if expressed as %; means should be accompanied by standard deviations (SDs) and medians by interquartile range (IQR). In text, use the following rule: spell out numbers up to nine and then use numerical designation for 10 and above.

5. All images must have minimum resolution of 300 dpi. The main figure heading should be in 10 point **bold**; legends should be single spaced in 10 point.

6. References should be indicated in the text sequentially in the Vancouver numbering style, as superscripted numbers after any punctuation mark.

7. Units of measurement, length, height, weight and volume are to be expressed in metric units (eg, metre - m, kilogram - kg, litre -L) or subunits. Temperature should be in degrees Celsius (°C); quantities of substances are given in moles (mol) and blood pressure is expressed as millimetres of mercury (mm Hg). All values of haematological, clinical and biochemical measurements use the metric system according to the International System of Units (SI units).

9. Abbreviations may be used for very long names, including those of chemical compounds. The full name should be given when first mentioned in the text unless it is a standard unit of measurement. If abbreviations are to be used in the Abstract, each should be explained when first mentioned in the text. Well-known abbreviations, such as DNA, AIDS, HIV, ADP, ATP etc, do not need to be introduced by the full name. Titles should include abbreviations only when the abbreviation is universally accepted.

10. Ethics. Consent statement and permission obtained by the institutional ethics committee (IEC). A cover letter should state that written informed consent was obtained from all subjects (patients and volunteers) included in the study and that the study was approved by the IEC. The name of the issuing ethics committee should be clearly disclosed, as well as its decision number and date of its issuing.

11. Acknowledgement. A statement listing all persons and institutions that has assisted the authors in performing the research in question.

12. Conflict of interest. A statement listing all cases of non-financial involvement of any author that could be perceived to be potentially damaging to the objectivity of the research project.

13. Financial disclosure. A disclosure state-

CONTENT

ment declaring any potential conflict of interest must be signed by each author. (See the policy statement on conflict of interest issued by the World Association of Medical Editors, WAME, www.wame.org or ICMJE uniform disclosure form for potential conflicts of interest, www.icmje.org.) This disclosure includes all affiliations or financial involvement (eg, employment, consulting fee or honorarium, gifts, stock ownership or options, travel/accommodations expenses, grants or patents received or pending and royalties) with any organisation having a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This information will be held in confidence while the paper is under review. If the manuscript is accepted for publication, the editors will discuss with the author how such information is communicated to the reader in the section "Conflicts of interest."

14. Data access. Statement on where and how the original data used to prepare the manuscript can be obtained.

15. Author ORCID numbers. After authors' names their initials should be listed and then the 16-digit ORCID numbers.

16. Author contributions. To qualify for authorship, one must made substantial intellectual contributions to the study on which the article is based (see Policy Statements - Authorship at www.wame.com). The author should participate at least in one of these three categories:

a. research question, conception and design, data acquisition and analysis,

b. statistical analysis, interpretation of data, provision of funding, technical or material support, overall supervision of the project.

c. drafting or critical revision of the manuscript.

In some research projects experts (such as biostatisticians or epidemiologists) may participate and although they may not be equally familiar with all aspects of the work (for example, some clinical variables or laboratory measurements), they may be qualified as the authors. A statement acknowledging contribution to the manuscript should be signed by all the authors. It will be published in the section "Author contributions." The corresponding author is responsible for the integrity of the work as a whole. It is dishonest to omit mentioning the investigator who had important engagement with some aspects of the work.

A pre-defined list of possible author contributions is given below. For each author one or more of the following 14 potential functions should be selected:

- Conceptualisation
- Methodology
- Software
- Validation
- Formal analysis
- Investigation
- Resources
- Data curation
- Writing - original draft
- Writing - review and editing
- Visualisation
- Supervision
- Project administration
- Funding acquisition.

After each of the applicable function, a colon (:) should be written, followed by the initials of the authors pertaining to this particular contribution (eg, Conceptualisation: AB, CD, Supervision: AB, XY, VW, etc).

17. Authorship statement. It should include the following:

a. A statement that the manuscript has been read and approved by all authors.

b. A statement that the authors confirm the sequence of their names in the order that will be reproduced in the article (if accepted for publication), listed after consecutive Arabic numbers.

c. The name of the corresponding author and a statement that they empower him/her to sign all the requested statements and to communicate with the Editorial Office on their behalf.

This statement should be signed by all the authors.

18. Cover letter. The letter accompanying the submission should include the following:

a. A statement that the submitted text is the result of the original work of the authors.

b. A statement that the paper has not been previously published, nor is it concurrently submitted to any other journal.

d. Assertion that written acknowledgements, consent statements and/or permission by the institutional ethics committee were obtained. The name of the ethics committee, the decision number and date should be included.

e. A brief description of the study, with accent on its novelty and why the authors believe that it should be published in *Scripta Medica*.

This letter should be signed by corresponding author.

The majority of these instructions are in accordance with "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" (www.icmje.org).

19. Submission of manuscripts. Manuscripts

CONTENT

and all enclosures (cover letter, authorship statement and financial disclosures) should be uploaded via the journal official website http://scriptamedica.com/submit-a-manuscript/.

20. Editorial process. Manuscripts deemed suitable for publication by in-house assessment will be reviewed by at least two outside experts. Contributors are encouraged to provide names of two or more qualified reviewers with experience in the subject of the submitted manuscript, but this is not mandatory. Galley proofs of the accepted articles will be sent to the corresponding author, who should reply within 48 h and either approve the galley proof for publication or mark the necessary corrections. The entire process, from the initial submission of the manuscript to the final review, including the sending and receiving of page proofs, will be completed online, vis the editorial platform SCIndeks.

21. Review procedure. Manuscripts suitable for peer review will be sent to at least two international reviewers, based on the topic of the manuscript and the potential reviewers' expertise. Reviewers will be allotted seven days to decide whether they will accept the invitation to review a manuscript or not, plus another seven days to write a review. In case of some delay, this may be extended for another seven days. In case that even then a review is not received, new reviewers will be invited instead. Some manuscripts may be accepted without revision, but if revision is required, the corresponding author must address each question, criticism and suggestion made by the reviewers or editor. He/she has 10 days to respond following the receipt of the reviewers' remarks. These topics should be addressed in a letter to the editor along with a revised manuscript. All the changes made to the text should be marked with a different colour, so that they can be tracked. Following receipt of a galley proof, authors are allotted a 48-h period to either approve it for publication or to suggest some changes.

The acceptance rate for *Scripta Medica* is around 40 %.

22. For further information, please contact the journal manager at the following address: slavica.serdar-janjus@med.unibl.org. For this purpose, the journal website http://scriptamedica.com/contact/ may also be consulted.

Specific instructions for a manuscript

Title page. The title page of the manuscript contains the title of the article, the full name of each author (without titles) and the departments and institutions of the author(s) in the order they are listed. The title page must also include the name of the corresponding author, (along with address, phone and e-mail address) to which the work should be attributed. The word count should be indicated, as well. Original articles may have up to 2.500 words, excluding abstract and references.
The title should identify the main topic or the message of the paper. The standard title of a research paper is a phrase (rarely a sentence) that identifies the topic of the paper; it should be concise and precise, informative and descriptive.
The title of a descriptive paper should include the necessary description, function, purpose, animal species or population. When a method is described, the title should indicate whether it is new or improved.

Abstract and key words. Structured abstract should be included in papers reporting original research. Abstracts are limited to 300 words in four labelled paragraphs: Background/Aim, Methods, Results and Conclusion. The abstract should state concisely the objectives of the study, methods used, results obtained and adequately answer the research question. The abstract should provide pertinent information when read alone. Abstracts should not contain any citing of references. Below the abstract, authors should provide 3-5 key words, according to the terms from the Medical Subject Headings – MeSH (www.nlm.nih.gov/mesh).

Introduction. Generally, this section provides the motivation for the paper (ie, what is missing or unknown in the research literature at this time), an overview of the scientific theory or conceptual models on which the research was based and the purpose of the study and why it is important. Cite only relevant references.

Methods. This section accurately describes the procedures used to carry out the study; it should be complete enough to permit others to replicate the study. Describe the methodological design, subjects, data sources, data collection methods and any statistical and analytical procedures. These five parts may not be needed in all papers. Short papers may include these details in different paragraphs, but titled subsections may be used in longer papers. The Methods section should describe how the research was structured, how subjects or groups of subjects (defined by sex, age and other characteristics) and how the subjects were chosen and assigned to

CONTENT

these groups. Identify all drugs and chemicals by generic names, exact drug dosages and routes of administration. Variability should be expressed in terms of means and standard deviations (SD). A p-value can be used to disprove the null hypothesis, but the authors should also give an estimate of the power of the study and state the exact tests used for statistical analysis.

Results. This section presents findings in logical sequence using the text, tables and figures. This section should show how the results of the study answer the research question. This may be shortest part of the entire paper. Details may be presented concisely in one or more tables or figures. Do not repeat the data presented in tables or figures in the text. Emphasise or summarise only important observations and how these answer the question posed in the introduction.

Tables. Each table with its legends, should be self-explanatory and numbered in Arabic numerals in order of their mentioning in the text. The title should be typed above the table and any explanatory text, including definitions of abbreviations, is placed below the table.

Figures. All figures (photographs, graphs or schemes) should be numbered with Arabic numerals in the order of their mentioning in the text. All lettering should be dark against a white background and of sufficient size to be legible when reduced for publication. Do not send original artwork, X-ray films or ECG tracings but rather photographs of such material. Images need to be at least 300 DPI (JPG or TIF files). Figure legends should be typed double-spaced on a separate page with Arabic numerals corresponding to the figure. All symbols, arrows, numbers or letters should be explained in the legend. An internal scale should appear on photomicrographs and methods of staining should be described in the legend.

Discussion. Discussion should be always written as a separate chapter and not together with the Results. Briefly state the principal finding that relates to the purpose or research question posed in the Introduction and follow the interpretation of the results obtained. Compare your findings with work reported previously by others. Discuss the implications of your findings and their limitations with respect to the methods used.

Conclusion. The conclusion should be brief and clear, answering the aim of the research and should not consist of repetition of the main results. Avoid unqualified statements and conclusions not completely supported by your data.

References. The reference list is the responsibility of the authors. List all the papers or other sources cited in describing previous or related research. Cite references in the text sequentially in the Vancouver numbering style, as superscripted number after any punctuation mark. For example: …as reported by Vulić and colleagues.[12] When two references are cited, they should be separated by comma, with a space. Three or more consecutive references are given as a range (eg, …as was published earlier.[12-14]). References in tables and figures should be in numerical order according to where the item is cited in the text. For citations according to the Vancouver style, see *Uniform Requirements for Manuscripts Submitted to Biomedical Journals*; this source gives the rules and formats established by the International Committee of Medical Journal Editors (www.icmje.org). The standardised abbreviations of the titles of scientific journals cited should be used. If there are six authors or fewer, list all six by last name, space, initials, comma. If there are seven or more, list the first three in the same way, followed by et al. For a book, list the editors and the publisher, the city of publication, and year of publication. For a chapter or section of a book, give the authors and title of the section, and the page numbers. For online material, please cite the URL and the date you accessed the website. Online journal articles can be cited using the doi number. Do not quote references within the Abstract and Conclusion section. All titles of cited manuscripts should be in English (the name of the original language should appear in brackets). Every effort should be done to add the doi number after the reference; if not available, PMID number should be listed. See examples below that conform to the Uniform Requirements for Manuscripts Submitted to Biomedical Journals:

- Miller AL, Evanson NK, Taylor JM. Use of donepezil for neurocognitive recovery after brain injury in adult and pediatric populations: a scoping review. Neural Regen Res. 2024 Aug 1;19(8):1686-95. doi: 10.4103/1673-5374.389628.
- International Committee of Medical Journal Editors (ICMJE). International Committee of Medical Journal Editors (ICMJE). Uniform Requirements for Manuscripts Submitted to

CONTENT

Biomedical Journals: writing and editing for biomedical publication. Haematologica. 2004 Mar;89(3):264. PMID: 15020262.

- Hull J, Forton J, Thompson A. Paediatric respiratory medicine. Oxford: Oxford University Press; 2015.
- Bydder S. Liver metastases. In: Lutz S, Chow E, Hoskin P, editors. Radiation oncology in palliative cancer care. Chichester (UK): John Wiley & Sons, Ltd.; 2013. p. 283-298.
- Christensen S, Oppacher F. An analysis of Koza's computational effort statistic for genetic program- ming. In: Foster JA, Lutton E, Miller J, Ryan C, Tet- tamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer; 2002. p. 182-91.
- Polgreen PM, Diekema DJ, Vandeberg J, Wiblin RT, Chen YY, David S, et al. Risk factors for groin wound infection after femoral artery catheterization: a case-control study. Infect Control Hosp Epidemiol [Internet]. 2006 Jan [cited 5 Jan 2007];27(1):34-7. Available from: http://www.journals.uchicago.edu/ ICHE/ journal/ issues/v27n1/2004069/2004069. web.pdf.

Review article

Review articles are written by individuals who have studied a particular subject or area extensively and who are considered experts. Narrative reviews and Systematic reviews should be identified as such in their titles. For these reviews, the word count should not exceed 2.500 words, excluding references and abstract. The manuscript may have up to 4 tables or figures and as many as 50 references. Any deviation from these limitations may be approved at the discretion of the Editor-in-Chief.

Current topic

Current topics are actually mini-reviews. They also review a certain topic, but less extensively and by quoting a considerably smaller number of original publications.

Special article

Special articles of 1500 words or less may be devoted to any medical problem, historic perspective, education, demography or contemporary issues. Up to 15 references may be cited and the piece may contain 2 tables or figures. An unstructured abstract in English (150 words or less) should accompany a specific article. Financial disclosure should be presented.

History of medicine

History of medicine articles deal with some historic aspects of medical research and practice. They should be considered as a type of a special article.

Case report

Case reports are most likely to be published if they describe any of the following: an unreported drug side effects (adverse or beneficial), drug interactions; a new, unexpected, or unusual manifestation of a disease; previously unsuspected causal association between two diseases; presentations, diagnosis and/or management of new and emerging diseases; an unexpected association between diseases or symptoms; an unexpected event in the course of observing or treating a patient, findings that shed new light on the possible pathogenesis of a disease or an adverse effect; a previously unknown disease. *Scripta Medica* does not publish instructive case reports, that is, presentations that make important teaching point of what is already well known but often forgotten.

Case reports (no longer than 750 words) should include the following: title, introduction, case history (including up to three figures) and discussion, references (up to six) and an unstructured abstract in English. The abstract may be a single paragraph containing no more than 100 words and followed by key words. Title should facilitate retrieval with electronic searching. Case presentation should include the history, examination and investigations adequately, description of treatments, all available therapeutic options that have been considered and outcomes related to treatments. Discussion includes the following: statement an unusual diagnosis, prognosis, therapy; report of a literature review of other similar cases; explain rationale for reporting the case; what is unusual about the case; could things be done differently in a similar case. There should also be a short conclusion.

Case reports may have as many as five authors. A very short case, about a particular disease can be submitted as a Letter to the Editor. Consent for publication must be obtained from the patients involved; if this is not possible, permission from a close relative or a legal guardian must be obtained before submission. Only non-identifiable data should be included, thus protecting the identity of the patient.

In a cover letter authors should indicate how the case report contributes to the medical literature. Submissions that do not include this information

will be returned to authors prior to peer review. For all case reports, informed written consent is required; the cover letter should state that consent was obtained. Authorship statement and financial disclosure should be presented.

Images in clinical medicine

The editors will consider original, clear and interesting images that depict new or "classic" clinical pictures submitted along with a descriptive paragraph of up to 200 words. The report may include two authors and three references. The authors must obtain a signed, informed consent from the patient or from a close relative or a legal guardian. The cover letter from the corresponding author should state that written consent was obtained.

Letter to the editor

If the letter refers to a recent journal article, it should not exceed 250 words, excluding references. All letters should be brief and to the point with no more than five reference citations. Figures or tables are not permitted in this format. Financial disclosure should be presented.

Editorial

Editorials are solicited by the editor to provide perspective on articles published in the journal and/or to express the general policies or opinions of the Editorial Board. Editor-in-Chief may invite a respectable scholar to write an editorial on a certain topic.

Submission of papers

Manuscripts, tables and figures should be submitted via the official journal website http://scriptamedica.com/submit-a-manuscript/, whenever it is possible, **all in one file. To assist the reviewing process, besides this full-text file, additional files should be uploaded, too:**

(1) Authorship statement, signed by all the authors (see above for details)

(2) Cover letter, signed by the corresponding author (see above for details)

(3) Title page, containing the manuscript title, full names and surnames (in this order!) and affiliations of the authors and the following seven statements/assertions:

- Ethics (number and date of issuing of the ethics committee – state its name – clearance or an explanation why it was waived of not sought at all)
- Acknowledgement
- Funding
- Conflict of interest
- Data access
- Author ORCID numbers
- Author contributions

All these data should be a part of the Title page, since they could reveal the identity of the authors.

(4) Body text, containing the title only and the rest of the manuscript with tables and figures (only this file is to be sent to reviewers in a double-blind manner) and

(5) Filled out WAME Manuscript Checklist (and MS Word form can be downloaded from the journal website)

Signed Authorship statement and Cover letter should be scanned and submitted electronically together with previous materials.

To minimise delays, we advise that you prepare signed copies of all statements before submitting the manuscript. In case of the incompleteness of the submission, the corresponding author will have to upload the missing documents within 48 h. Failure to comply to this deadline will result in the rejection of the submitted manuscript, based on its incompleteness. In such a case, the authors can start a new submission.

CONTENT