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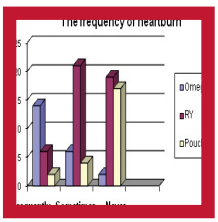

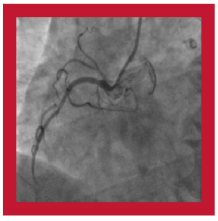

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EDITORIAL

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An Advice for Young Researchers

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For a young researcher, the best way to improve his skills and develop his research capabilities is to work in established research laboratories where he is enabled to learn modern techniques and how to attack the scientific problems. Today, we have easy communications, including computers and the internet, but direct interactions with the most experienced scientists are the best way for young scientist to advance his research capabilities. Ulf Svante von Euler, Swedish pharmacologist and physiologist presents the best example that illustrates how interaction of a young researcher with established scientists develop his research capabilities and become a well-known scientist[1].

When Ulf was seventeen (1922), he came in Stockholm to study medicine. As a student, he became interested in research, and in 1926 he attended the Twelfth International Congress of Physiologists in Stockholm where he heard lectures by I. P. Pavlov, E. H. Starling and other great scientists of the time. He also observed a historic demonstration by Otto Loewi on the existence of Vagusstoff in the frog's heart, which would stimulate his own interest and research on mediators of nerve transmission. Prior to this demonstration, Loewi had published several papers on the nature of this chemical substance that slowed the heart, but not all of his research contemporaries were convinced. However, a successful demonstration at the Congress (repeated eighteen times) convinced all critics. Von Euler recalled that these experiments inspired his enduring interest in neurohumoral transmission.

Initially, von Euler was influenced by several well-known Swedish scientists: G. Liljestrand (pharmacologist/physiologist), R. Fåraeus (a hematologist) and H. Theorell (a biochemist, who received the Nobel Prize for Medicine and Physiology in 1955). Ulf defended his doctoral dissertation in 1930 and became a professor of pharmacology. Then, he received a two-year scholarship for postdoctoral studies abroad that enabled him to improve his skills by working with several famous foreign researchers.

The young Ulf von Euler made the most of this opportunity. He spent six months in Hampstead at Sir Henry Dale's laboratory, two months in Birmingham with I. de Burgh Daly, eight months in Ghent with C. Heymans, and three months in Frankfurt with G. Embden. Later, in 1934, he returned to London for six months to work with A. Hill, primarily because Liljestrand advised him instead of pharmacology, rather to devote to physiology because at that time in Sweden this scientific discipline was more appreciated. Towards the end of 1937, he went back to Hampstead for five months to work again with Sir Henry Dale.

Key words: history of medicine, pharmacology, psysiology, neurohumoral transmission, substance b.

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Pharmacologists vs Neurophysiologists

At the time, two separate camps of researchers held differing views on how nerve impulses were transmitted to effectors sites including nerves, glands and muscles. The battle between these two groups of scientists–the neurophysiologists and the physiologists–lasted for more than a quarter of a century. The prominent pharmacologist/physiologist, Henry H. Dale (1875-1968), provided early evidence for neurohumoral transmission. From the 1930s, the neurophysiologists led by John Eccles, studied electrical phenomena in nerves with an oscilloscope. They thought that chemical neurotransmission was too slow to cause the rapid response of skeletal muscles after nerve stimulation. But evidence for chemical neurotransmission continued to accumulate. The pharmacologists of which von Euler was a member declared victory when Paul Greengard described the molecular mechanisms involved in chemical transmission of the nerve impulse. He established two types, fast and slow; the rapid chemical mechanism occurs in less than a millisecond, and transmission of the slow type lasts for a few milliseconds. However, studies in the central nervous system provided a support for neurophysiologists view. The rise of electron microscopy revealed "tight junctions" in some brain areas, which reinforced the idea of electrical transmission across nearly non-existent spaces.

Most important discoveries done by von Euler

In Henry Dale's laboratory, von Euler worked with John H, Gaddum. They discovered substance P. Nearly forty years later this polypeptide composed of eleven amino acids was isolated, sequenced and synthesized. When discoverers isolated this active substance, they labeled "P" for the preparation. After von Euler returned to Stockholm in 1939, he discovered in sheep prostate glands new substance prostaglandin. As a postdoctoral fellow in Sir Henry Dale's laboratory, he used bioassays of adrenaline and other active substances to study sympathetic neurons. He then isolated noradrenalin-containing vesicles from sympathetic neurons by centrifugal separation and published several important papers on neurohumoral transmission in sympathetic nerves. Initially, not everyone accepted his findings, but many prominent researchers subsequently confirmed his results. He established that noradrenalin was a sympathetic neurotransmitter, and in 1970 he shared Nobel Prize in Physiology and Medicine with Julius Axelrod and Bernard Katz.

Von Euler shared his experiences with other scientists

Professor von Euler generously shared his experiences with many other scientists, including those in United Kingdom, Germany, Argentina, Yugoslavia, Canada, and USA. He visited Yugoslavia three times. In 1961, Professor Pavao Stern organized a symposium on substance P in Sarajevo, where he brought together a number of leading researchers in the field, including von Euler (Fig.1) and Gaddum, who discovered this biologically active neuropeptide. There were 25 participants at the Sarajevo symposium but von Euler's and Gaddum's mentor, Henry Dale, who was 86 at the time, was unable to make the trip to Sarajevo. Professor Pavao Stern's symposium (Fig.2) not only facilitated the sharing of information between foreign and domestic scientists but also stimulated further research on the effects of Substance P in the central nervous system. Von Euler came to Belgrade in 1968 to attend an international symposium on occasion of the 50th anniversary of the Belgrade Medical School. I meet him there and talked to him. He asked many detailed questions about my own research on acetylcholine in pigeon's brain and a new method that I developed for estimation of "free" and "bound" acetylcholine. He suggested me to publish my findings in a good international journal, and to join some established foreign laboratory. I followed his advice and published in the *British Journal of Pharmacology*[2], *Canadian Journal of Physiology and Pharmacology*[3], and *Neurophysiology*[4]. Also, in 1970 I left Sarajevo and joined the most active peptide laboratory in the USA, where worked for two years with Ervin G. Erdos[5]. In 1982, von Euler was my guest at the Department of Pharmacology. He intended to help us to build an international medical research center in Tuzla (Fig.3). Unfortunately, he dpied the following year.

Figure 1. U.S. von Euler at the substance P symposium, Sarajevo, Jun 9th and 10th, 1961. Photo: F. Lembeck.

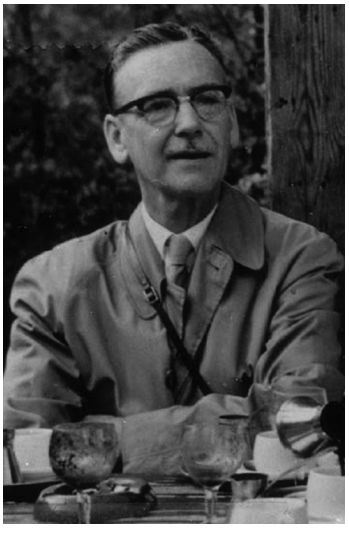


Figure 2. **Participants at the symposium on substance P (held in Sarajevo, June 9th and 10th, 1961). The symposium was presided by Professor Pavao Stern from the Institute of Pharmacology and Toxicology, Sarajevo. Standing: M.P. Milošević (second from the right), U.S. von Euler (third), S. Huković (fourth), K. Lissak (fifth), P. Stern (sixth). This photo was taken by John Gaddum. I found it among the discarded papers from the Professor Stern's office after his death.**

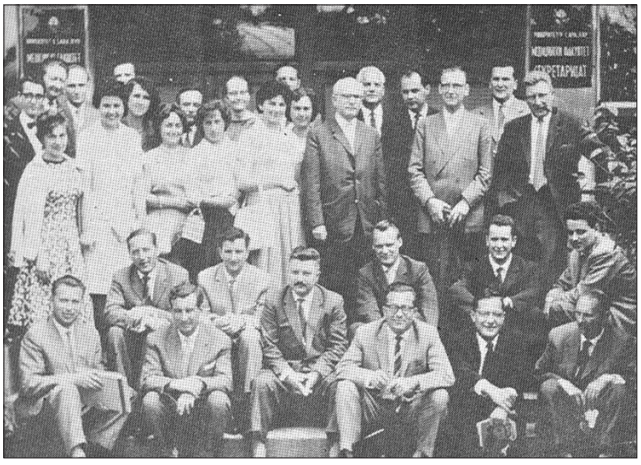
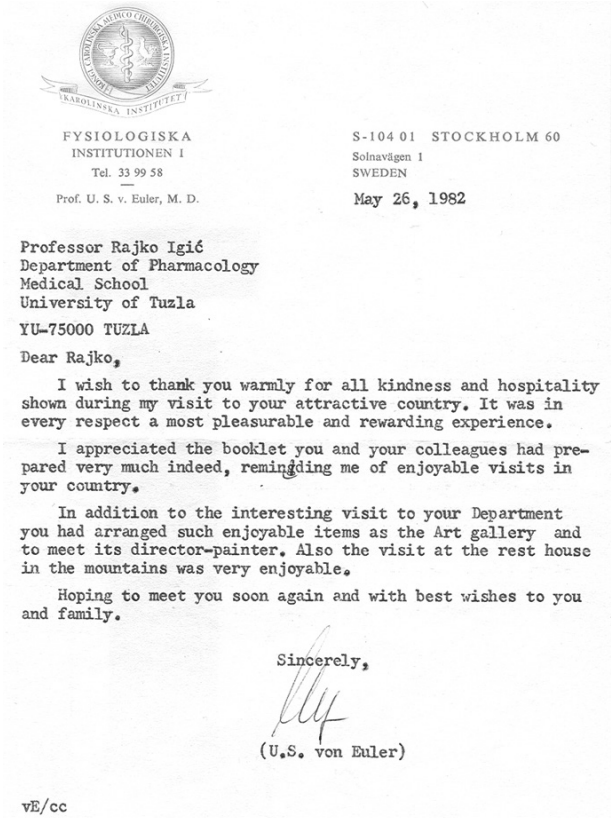


Figure 3. **The last letter I received from Ulf Svante von Euler**



FYSIOLOGISKA INSTITUTIONEN I
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S-104 01 STOCKHOLM 60
Solnavägen 1
SWEDEN

May 26, 1982

Professor Rajko Igić
Department of Pharmacology
Medical School
University of Tuzla
YU-75000 TUZLA

Dear Rajko,

I wish to thank you warmly for all kindness and hospitality shown during my visit to your attractive country. It was in every respect a most pleasurable and rewarding experience.

I appreciated the booklet you and your colleagues had prepared very much indeed, reminding me of enjoyable visits in your country.

In addition to the interesting visit to your Department you had arranged such enjoyable items as the Art gallery and to meet its director-painter. Also the visit at the rest house in the mountains was very enjoyable.

Hoping to meet you soon again and with best wishes to you and family.

Sincerely,

(U.S. von Euler)

vE/cc

Conclusion

Ulf Svante von Euler's scientific achievements show how a young researcher can develop and enhance his research capabilities. In several established research laboratories, he learned the most modern techniques and how to attack prominent scientific problems of the time. Later on, he shared his experiences with many other scientists. Direct interactions between junior and established scientists enable young scientists to develop their skills and better contribute to science. Thus, we need to increase continuing exchange programs financed by governments, organizations that support science, and universities. Greater scientific progress in both developed and developing countries will be the ultimate reward for such activities.

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REVIEW ARTICLE

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The Importance of Rehabilitation Treatment in Patients with Parkinson's Disease

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SUMMARY

Parkinson's disease (PD) is a chronic neurodegenerative disease with a slowly progressive course, having an average duration of about 15 years. It is characterized by akinesia/ bradykinesia, tremor, rigidity and postural instability. For the diagnosis of PD at least two of these four characteristics are required. There is a whole spectrum of non-motor symptoms (mood disorders, different levels of cognitive deficit, sleep disorders, fatigue, autonomic dysfunction). The patomorphologic base of PD is a disorder of the nigrostriatal dopaminergic mechanisms, metabolic damages, structural changes (hydrocephalus, tumors) or degenerative processes of presynaptic nigrostriatal dopaminergic projections or the striatum. Although the pharmacological approach is still essential, more systematic reviews and meta-analysis support the hypothesis on the positive effects of physiotherapy and intensive kinesiotherapy in PD patients. The main rehabilitation method for these patients is kinesiotherapy in its various forms, related to the individual therapeutic target, based on functional limits. Rehabilitation programs contain kinesiotherapeutic procedures for balance, posture, the range of motions- especially rotation of the trunk, strength, elongation, as well as exercise for functionally reduced motion types. The greatest emphasis in the rehabilitation process should be on the re-education of gait, which involves the optimization of initiation, speed, and length of steps. The aim of kinesiotherapy and occupational therapy is to bring the maximum functional independence of the patient and the occurrence of complications to a minimum.

In neurodegenerative disorders, all modalities for improving the gait function are essentially a lifelong activity. Therapeutic strategy comes down to the combination of pharmacotherapy and neurorehabilitation methods.

Key words: Parkinson's disease, neurorehabilitation, gait.

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1. Definition and patophysiological basis of Parkinson's disease

Parkinsonism is a clinical syndrome characterized by akinesia/ bradykinesia, tremor, rigidity and postural instability. For the diagnosis of this syndrome at least two of these four characteristics are required. Patomorphological basis of this syndrome is a disorder of nigrostriatal dopaminergic mechanisms, whether it comes to the discharge of synapses (reserpine, tetrabenazine), to the block the dopamine receptors in the striatum (neuroleptics), metabolic damages, the structural changes (hydrocephalus, tumors) or degenerative processes of the presynaptic nigrostriatal dopaminergic projections or the striatum itself.[1]

Accordingly, parkinsonism is classified as a primary, idiopathic Parkinson's disease (PD), secondary or symptomatic, so-called "parkinsonism- plus" syndromes, parkinsonism within the neurodegenerative disease, and psychogenic parkinsonism.[2]

PD is a chronic neurodegenerative disease with a slowly progressive course, with an average duration of about 15 years. This is the second most common neurodegenerative disease, right after Alzheimer's disease, and certainly the most common form of parkinsonism. In about 75% of cases of parkinsonism, the idiopathic form of Parkinson's disease is present.[3,4]

It is believed that Parkinson's disease affects 0.3% of the world population. Based on the data of the European Association of Parkinson's disease 6.3 million people worldwide suffer from PD, but when it comes to Europe, available statistical data show the number of 1.2 million patients. The incidence and prevalence increase exponentially with age so after 65 years of age 1% of people have Parkinson's disease.[3,4]

The onset of PD can be observed at any age- rarely before 30 years of age, in 5-10% the onset occurs before 50 years of age, and in 50% before 65 years of age. Most commonly the disease starts after 60 years of age, and with a higher incidence in men (ratio of men and women 3:2).[5,6]

Clinically, the motor symptoms of PD appear when 60-80% of striatal dopaminergic terminals and 40-50% of the neurons in substantia nigra- pars compacta are lost. The observation that a massive dopaminergic denervation occurs before the early symptoms of PD is explained by the compensatory presynaptic and postsynaptic mechanisms in nigrostriatal dopaminergic system.[7]

Three basic pathological findings in PD include:

1. The loss of dopaminergic neurons in the pars compacta of the substantia nigra (loss of 50% of these neurons causes the expression of the motor symptoms of the disease); the extinction of these neurons in patients with PD is 8-10 times faster than during normal aging and is most prominent in the first five years of the disease. It is considered to achieve the plateau after ten years of the disease duration. The degeneration of mesolimbic pathway leads to mood disorder, while the degeneration of mesocortical pathway leads to cognitive disorder. Progressive neurodegeneration also affects the non-dopaminergic neurons with a consequent deficit of other neurotransmitters besides dopamine, such as serotonin, noradrenaline, acetylcholine, and the manifestation of a whole series of symptoms such as mood and behavioral disorders, cognitive disorders.[8]

2. Reduced levels of dopamine in the striatum, especially at the level of the putamen, where nigrostriatal fibers project (with a reduction of over 80% of normal values).[9]

3. Lewy neurites and Lewy bodies are intracellular protein inclusions, with alpha-synuclein as their base, which is in physiological conditions present in a significant concentration at the level of the neurons and is related to the normal function of synapses and the processes that are relevant to neurodegeneration. It is assumed that there is a problem with the processing of this protein which, when found in appropriate circumstances, shows a strong tendency to form aggregates (Lewy bodies).[10]

In most cases, a sporadic or idiopathic PD is present, and age is the only defined risk factor for its occurrence, whereas 10-20% of involved patients have a genetic (autosomal dominant and recessive) form of PD.[11] domain.

2. The clinical presentation of Parkinson's disease

Characteristic clinical features of Parkinson's disease involve the presence of motor symptoms of the disease and a whole range of non-motor manifestations.[12,13] Non-motor symptoms in PD include mood disorders (primarily apathy, depression and anxiety); various degree of cognitive decline (from the level of mild cognitive impairment to dementia); and various forms of sleep disorders (sleep fragmentation, REM sleep disorders, sleep apnea, excessive daytime sleepiness); sensory disturbances (pain, dysesthesia); fatigue, autonomic dysfunction (constipation, urinary problems, sexual dysfunction, temperature dysregulation, orthostatic hypotension, profound sweating).[14]

In the comprehensive understanding of the PD symptoms, it was observed that motor signs in the PD were often preceded or were associated with non-motor symptoms.

2.1 Clinical forms of Parkinson's disease

Clinical forms of the PD include tremor and non-tremor form of the disease: akinetic-rigid form and a form with postural instability and gait disorder (Postural Instability Gait Disorder- PIGD), as well as the mixed form of the PD.[15] Generally, hyperkinetic form of PD is characterized by a worse response to applied levodopa, but has a slower course and progression. In contrast, in the case of a hypokinetic form of the disease, the response to the therapy is better, but there is a faster progression of the disease with the occurrence of dementia, and psychiatric complications of the therapy at an earlier age.[16]

2.2 Motor symptoms of Parkinson's disease

The cardinal symptoms of the disease are motor symptoms, which include tremor, rigidity, and bradykinesia; usually in the later stages of the disease there is a development of postural instability.[17]

Tremor is the strongest predictor of PD and it is a resting tremor, most often in combination with the postural or kinetic tremor of extremities, primarily distally. It is present in approximately half of the patients; in 69% of patients, tremor is an initial sign of the disease, although about 15% of patients with PD never develop tremor during the course of the disease. Tremor does not have to get worse during the disease and about 9% of patients lose tremor during the disease. Tremor is not considered as a pure dopaminergic sign and severity of its manifestations does not correlate with dopamine deficiency in the striatum, and it is different and often has a quite disappointing response to levodopa and dopamine agonists.[18]

Bradykinesia is the most cardinal symptom of Parkinson's disease. It represents the slowness in initiating of voluntary movements and the progressive reduction of the speed and amplitude of the same, repetitive movements. The severity of clinical manifestations of bradykinesia correlates with the degree of nigrostriatal damage. It changes in conditions such as stress or sudden stimuli, which indicates the preservation of motor programs that can not be otherwise run except as a reaction to the external stimuli.[18]

Rigidity is muscle hypertonia, which manifests both proximally and distally, affecting evenly agonistic and antagonistic muscles. It is present in more than 90% of the patients with PD and correlates to the deficit of dopamine in the striatum.[18]

Postural instability, due to the loss of postural reflexes, is usually manifested in the later stages of the PD, usually not prior to the third stage according to Hoehn and Yahr classification. However, in early stages of PD patients have a lower stability limit of the body which is referred to as compensated intraclinical postural instability.

In addition to these cardinal motor symptoms, during the course of the disease a whole range of other motor manifestations of PD appear in the form of gait disturbances and falls, positional deformities, and also disorders of speech and swallowing.[19]

2.2.1 Gait abnormalities in Parkinson's disease

Gait abnormalities (reduced speed, shortened length of the step, reluctance prior to the start of stepping, a longer period of relying on both feet) are an integral part of the clinical manifestations of Parkinson's disease and significantly disable a patient and determine the poor quality of life.[20] In addition, the disorder of rhythmicity of the gait is manifested, the inconsistency of the locomotor form, with a marked variability in length and time duration of the step ("stride-to-stride variability"), which is considered to be a parameter of a higher risk of falls. Problems are particularly pronounced while the patient turns, caused by axial rigidity and lack of intersegment flexibility, where patients turn as a block that often leads to falls.[21] Parkinson's gait is slowed, with reduced step length during the gait cycle, decreased cadence-the number of steps per minute, and on the other hand, there is an extended period of stride in contact phase.[22] Ranges of motions in hips, knees, and ankles are reduced mainly due to the rigidity and reduced extension in the joint. The swinging of arms is significantly reduced or not present at all, trunk rotation is carried out in a block with the pelvis. Patients stand with pronounced flexion of the spine and neck, moderate flexion of elbows and slightly flexed feet. The position of generalized flexion is often more pronounced during walking.

A huge problem in gait are blocking episodes of "freezing" in gait, especially when turning and encountering obstacles, walkways and entrances.[22]

Initiation of gait includes the period of preparation for the movement and execution phase of the movement. In PD patients, preparation time is significantly prolonged, with a tendency for further extension as the disease progresses. The execution phase of the movement is also extended but to a lesser extent.[23] During initiation, walking posture is adjusted by moving the center of

gravity, which is achieved when moving the center of gravity towards the front by flexion of the trunk and ankle. In PD patients, particularly in advanced stages, the move of the center of mass-gravity is slowed.[24] In addition to the slowdown in the front adjustment of the center of the mass, there is a reduced lateral shift of the body mass over the stance limb, decreased propulsive forces and prolonged anticipatory postural adjustments. Length of the step can become normal when using visual guides and auditory rhythms, also the walk performance deteriorates when there is a distracting task during walk.[25,26]

Festination is the disturbance in gait pattern typical for PD, and less frequently seen in parkinsonism. The main characteristics are fast, small steps in an attempt to keep the center of gravity between the foot while the trunk is reluctantly leaning forward, with the center of gravity shifted forward. In order to compensate the instability and prevent the fall, patient increases the speed of walking and shortens the stride length.[27,28]

PD characteristically starts asymmetrically, first affecting one side of the body, on which signs of the disease are more prominent throughout the duration of the disease. In the further course, there is a disturbance of posture, followed by the progression on the other side of the body, whereas in the later stages postural reflexes are also affected, followed by postural instability. At the end, the patient becomes severely physically disabled, confined to a wheelchair or bed.

3. Clinical assessment of PD

Stage of the disease is determined based on the scale of Hoehn and Yahra[29], which primarily described five stages of the disease, and later was modified with additional stages 1.5 and 2.5 of the disease. Stage 1: disease affects one side of the body; Stage 1.5: The single-sided plus axial involvement; stage 2: Bilateral disease without any disturbance of the balance; Stage 2.5: Mild bilateral disease with recovery on pull test; stage 3: Mild to moderate bilateral disease; some postural instability; physically independent; Stage 4: Severe disability; still able to walk or stand unassisted; Stage 5: Wheelchair-bound or bedridden. According to this scale, stage 3 is considered critical (loss of balance) and indicates a worse prognosis, significantly higher risk for dementia and death.

The severity of PD is estimated on The unified Parkinson's disease rating scale (UPDRS).[30] This scale consists of four sub-scales: the first one estimates thinking, mood and behavior, the second is related to the daily activities, the third presents a motor overview of parkinsonism symptoms, while the fourth estimates complications of PD therapy. A higher sum of values of these scales corresponds to the worse clinical symptoms of the disease.

For the purpose of behavioral assessment and determination of the most common disorders of mood and behavior, Hamilton anxiety rating scale and Hamilton rating scale for depression are used.

Hamilton Anxiety Rating Scale (HAM-A)[31] is a scale with 14 items, which enables estimation of psychical and somatic anxiety: 13 questions and an observation by the examiner on the behavior of the patient during the test, and the scoring of each response to the scale of zero to four, where a higher score indicates a higher degree of manifested anxiety. The total score ranges from 0 to 56: mild anxiety- total score = 18, moderate anxiety - total score = 25 and severe anxiety - total score = 30.

Hamilton Rating Scale for Depression (HRSD), also known as HDRS or HAM-D[32], is used to determine the severity of manifested depression. The original version consists of 17 items (HDRS17). A total score implies: 0-7 = no depression; 8-15 = minor depression and score 10 or more = major depression.

In order to assess cognitive impairment, the Mini-Mental test (MMSE)[33] and the Clinical scale for the assessment of dementia are used. Mini-mental test in standard form (MMSE) was defined by Folstein in 1975 and it is a short structured test, which can be applied for an initial evaluation of the cognitive status of the patient, as well as for its further cognitive monitoring. It includes the interview with the patient and examines the functions, including arithmetic, memory and orientation (temporal and spatial orientation), attention, comprehension, speech understanding, reading, writing, drawing, and arithmetics. The score implies: 30-27 = cognition maintained; 26-24 = mild cognitive disorder; 23-18 = mild dementia; 17-11 = moderate dementia; 0-10 = severe dementia.

Clinical dementia rating scale (CDR)[34] includes scoring of six cognitive domains: memory, orientation, evaluation and problem-solving skills, social role, hobbies, and the possibility of keeping an account of themselves. The final score is computed by an algorithm and is assigned as: CDR- 0 (normal); CDR- 0.5 (very mild dementia- mild cognitive impairment), CDR-1 (mild dementia); CDR- 2 (moderate dementia); CDR- 3 (severe dementia)

4. Rehabilitation in Parkinson's disease

Modern rehabilitation is holistically oriented, and includes

medical, psychological, and social dimensions and it rests on the foundation of teamwork. It is impossible to achieve restitution of activities, social participation, and improving the quality of life in patients with Parkinson's disease through the action of a single profession. In order to optimize the effect of rehabilitation, it is necessary to consolidate a variety of health and non-health professions: physiatrists, physiotherapists, occupational therapists, nurses, psychologists, logopedist, social workers, and institutions that provide and approve the necessary health care.

Rehabilitation is a complex and comprehensive process because the violation of the physical integrity also carries changes in the emotional and social functioning of a person. The occurrence of physical damage may lead to changes in a person's self-perception, professional and family roles, and changes in social status. Priority role of psychologists in the rehabilitation is to assess all mental strengths and potential, so that the patient reaches the maximum, in relation to its current state. An individualized approach to the patient makes it possible to observe all his skills, personality traits, and social functioning, and accordingly schedules an appropriate treatment.

Changes in health status can affect family relationships, work ability and overall quality of life which a patient had before the disease. The role of a social worker is to help the patient and family to adapt to new environmental conditions. Based on interviews (socio-anamnestic interview) with the patient, family and other people in the patient's environment that are important for his recovery, social worker assesses the current needs and with the patient/ family develops a treatment plan.

Although the pharmacological approach remains essential, more systematic reviews and meta-analysis support the hypothesis about the positive effects of physiotherapy and intensive kinesiotherapy on the condition of patients with PD.[35,36] In their essence, as main ideas, these studies have focused neurorestoration, neuroprotection and slowing the disease progression.[37]

A series of studies over the past decade concluded that the exercises in a structured medical form could slow, stop or even lead to reversion of neurodegenerative processes and encourage neurorestoration of compromised nerve pathways. It is pointed to the possibility that the therapeutic exercise can induce production of glial neurotrophic factor (GDNF) in the substantia nigra where the dopaminergic cells are situated, which is related to neurodegenerative and neuroprotective mechanisms induced by the training.[38,39]

On the other hand, inactivity leads to a possible prodegenerative effect, and physical inactivity is even cited as a possible factor, but also a catalyst in the pathogenesis of Parkinson's disease.[40] In studies in animal models of Parkinson's disease the beneficial effects of exercise on neuroplasticity are confirmed, even with a neuroprotective effect, with slowing the progression of the disease.[41,42]

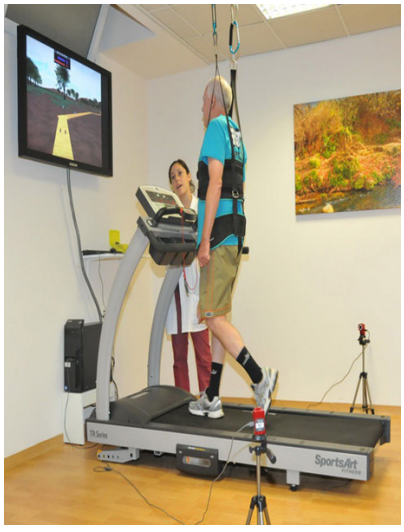
The main objective in the rehabilitation of patients with PD is to improve, maintain or delay the deterioration of gait, which in fact implies the possibility for a rapid change in motor activity or motor task (program) when conditions in the external environment change, as well as the possibility for a safe gait during various motor and cognitive tasks. Depending on the phase of PD, design of the gait rehabilitation must take into account the timely different form of progress of motor and non-motor symptoms of the disease, which affect the gait quality.[43] Mobility requires the dynamic neural control and the possibility of effective adaptation of movement, control of balance and postural transition during the changes in the environment and specific tasks. Clinical relevance of impaired gait and balance in PD is essential and a key factor which leads to falls, injuries, fractures, and immobility, significantly impairs quality of life, accelerates disease progression and reduces survival.

During the design of the gait rehabilitation in patients with PD, all functional elements that affect mobility must be taken into account. In the gait training, techniques with auditory or visual guides are used, for which researches have shown that they contribute to gait facilitation, and then, if the results of gait pattern are satisfactory, these guides are gradually excluded, with further accentuation of the proprioceptive training which potentiates the sensorimotor integration of the PD patients. They are taught to increase the speed and amplitude of stride in a protective gait pattern.[43]

In recent years, as a part of the rehabilitation concept, aerobic training is more and more recommended, especially the therapeutical training on treadmill tape, which led to improved gait in more treadmill studies in patients with PD.[44,45] All of these elements are joined by tested concepts with different forms of "guides" - techniques that help to keep the proper rhythm and direction of gait, which is of fundamental importance in gait rehabilitation.

Figure 1. Gait training using visual guides

Figure 2. Gait training on a treadmill tape



The main method of the rehabilitation of patients with PD is kinesiotherapy in its various forms and in relation to the individual therapeutic target which is based on functional limits. Rehabilitation programs contain kinesiotherapeutic procedures for balance, posture, the range of motions (especially rotatory motions of the trunk), strength, as well as for functionally reduced forms of motion, taking into account the extent and progression of the disease. Functional strength training may be used to increase muscle strength, in particular, extensors of lower limbs and back and the postural control (thoracic stabilizers, hip and knee extensors, anterior tibial muscle and gastrocnemius muscle). Traditional stretching techniques can be used for elongation of shortened flexors of the hip, knee and plantar flexors. Activities for weight shifting provide more opportunities for the integration of functional strength and postural reactions in the movement pattern.[46]

Due to the degenerative nature of the disease, the goals of the program of physical activity are the preservation of muscle function for movements involved in everyday activities. Generally, types of physical activities such as exercises for general coordination and balance are considered, and also relaxation exercises that can reduce muscular incoordination, and tremor. Exercises aimed at maintaining postural strength and flexibility should also be components of the plan and program of the physical activity.[47,48]

Figure 3. Exercises for balance improvement

Figure 4. Stretch and strength exercises

Although kinesiotherapy is the basis of rehabilitation of PD patients, other physical therapy modalities can contribute to alleviating the symptoms of the diseases, such as thermotherapy (to reduce rigor), hydrokinesiotherapy, and electrotherapy.

Transcranial magnetic stimulation (TMS) is a non-invasive neurostimulative and neuromodulatory technique, based on the principle of electromagnetic induction of the electric field in the brain. Short-term, strong magnetic field, emitted above the scalp, passes through the structure of the scalp and induces small, varying electricity in the targeted telencephalic areas. This local electric field can be of sufficient intensity and density to depolarize neurons. When the TMS pulses are applied repetitively (repetitive TMS - rTMS) they can modulate cortical excitability (lowering or raising it), depending on the parameters of the stimulation, even longer than the length of the stimulation.It is believed that rTMS in patients with PD operates in two ways: by increasing cortical excitability of thalamocortical pathways, which is considered to be reduced in PD patients, and modifying the metabolism of a catecholamine in subcortical areas via the cortical stimulation. Besides the effect on the improvement of motor function, it has been shown that rTMS has a good therapeutic the effect on depression, that is present in about 50% of patients with Parkinson's disease.[49]

An important role in the rehabilitation of these patients also has occupational therapy, with the aim to help the patient to be more independent in activities of daily living. The occupational therapist works with the patient in increasing of the mobility, prevention of falls, transfers, activities in bed, self-care activities (training of feeding, dressing, personal hygiene), overcoming of architectural barriers and performs the advisory work with the patient and family, regarding the adaptation of living space.The aim of kinesiotherapy and occupational therapy is to bring to the maximum independent functioning of the person and minimize the occurrence of complications. The strategy for movement includes launching education and re-education of the person about carrying out activities such as: turning during gait, turning in bed, getting up and going to bed, getting up and sitting down on a chair, reaching for objects etc. It is important to recognize the resulting compensation and act upon it.

Contemporary neurorehabilitation approach emphasizes the concept of a highly individualized structured rehabilitation program that includes diagnostics and rehabilitation of gait with an integrated kinesiotherapeutic program that includes various types of exercises and training whose therapeutic targets are defined by functional limits, for each patient individually. For each patient, a specific dosage and progression of training are determined, both in quantity and in severity, to overcome challenges of movement in the environment.

In neurodegenerative disorders, all modalities for improving the gait function are essentially a lifelong activity. Therapeutic strategy comes down to the combination of pharmacotherapy and neurorehabilitation methods.

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Značaj rehabilitacije u liječenju pacijenata oboljelih od Parkinsonove bolesti

SAŽETAK

Parkinsonova bolest (PB) predstavlja hronično neurodegenerativno oboljenje sa sporo progresivnim tokom, čija je prosječna dužina trajanja oko 15 godina. Karakteriše se akinezijom/bradikinezijom, tremorom, rigiditetom i posturalnom nestabilnošću, sa tim što je za postavljanje dijagnoze ovog sindroma potrebno bar dva od četri znaka. Prisutan je i čitav spektar nemotornih manifestacija (poremećaj raspoloženja, različit stepen kognitivnog deficita, poremećaj spavanja, zamor, autonomna disfunkcija). Patomorfološka osnova ovog sindroma je poremećaj nigrostrijatnih dopaminergičkih mehanizama,metabolička oštećenja, strukturne promjene (hidrocefalus, tumori) ili degenerativni procesi koji zahvataju presinaptičke nigrostrijatne dopaminergičke projekcije ili sam strijatum.Mada je farmakološki pristup i dalje esencijalan, više sistematizovanih pregleda i meta analiza podržava hipotezu o pozitivnim efektima fizioterapije, a unutar nje i intenzivne kineziterapije na stanje bolesnika sa PB.Glavna metoda u rehabilitaciji bolesnika od PB je kineziterapija u svojim različitim formama u odnosu na pojedinačni terapijski cilj koji je zasnovan na funkcionalinim limitima. Rehabilitacioni programi sadrže kineziterapijske procedure za balans, posturu, obim pokreta, naročito onih rotatornih pokreta u trupu, vježbe snage,istezanja kao i vježbe za funkcionalno redukovane obrazce pokreta. Najveći naglasak u procesu rehabilitacije trebao bi biti na reedukaciji hoda koja podrazumijeva optimiziranje iniciranja, brzine i dužine koraka. Cilj kineziterapije i radne terapije je do maksimuma dovesti samostalno funkcionisanje oboljele osobe, a pojavu komplikacija svesti na minimum.

U neurodegenerativnim poremećajima svi modaliteti za poboljšanje funkcije hoda u suštini su doživotna aktivnost. Terapijska strategija se svodi na kombinovanje farmakoterapije i neurorehabilitacionih metoda

Ključne riječi: Parkinsonova bolest, neurorehabilitacija, hod

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Bone Metabolism Markers and their Correlation with Body Mass Index in Aerobic Physical Activity

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ABSTRACT

Introduction: Bone formation marker osteocalcin (OC) and bone resorption marker C-terminal telopeptide of type 1 collagen (CTX) can be used to detect or to monitor the early responses of the skeleton to physical activity. Literature suggests that it is likely that higher body mass index (BMI) has positive effect on bones and can postpone onset of osteoporosis.

Aim of the Study: The aim of this study is to:
1. Determine the effect of aerobic physical acitivity on OC and CTX in young women
2. Investigate correlation of OC, CTX and BMI in young women engaged into structured aerobic excercise

Material and methods: Study included 64 healthy young women, aged 19 to 25 years, devided into two groups: intervention group (n=32) and control group (n=32). The study duration was six weeks with follow-up period of four weeks. The intervention group underwent structured aerobic physical activity program for six weeks, but the control group did not receive such program. Level of OC, CTX and BMI were measured at baseline, after 6-week aerobic program, and after 4-week follow up (only intervention group).

Results: There was significant increase of OC level after 6-week aerobic program, while level of CTX did not changed. OC level was at its maximum immediately after finishing the program in the participants with normal BMI ($p<0.001$). There was no statistically significant interaction of BMI and CTX level.

Conclusion: Aerobic physical activity increases level of osteocalcin, suggesting that it has positive influence on bone formation in young women, primarily in women with normal BMI.

Key words: osteocalcin, C-terminal telopeptide of type 1 collagen, bone metabolism, aerobic physical activity

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Introduction

A Bone remodeling involves two continuous processes that occur as a result of body weight and physical activity: bone resorption and bone formation. These two processes are essential in maintaining skeletal homeostasis. Physical deformation of the bone cells, achieved by physical activity, is essential for maintenance of bone strength. Bone adapts its form to meet the physical demands placed on it by changing its size and density.[1] The body weight and potential energy from the earth's gravity will pass through the bones and joints, forcing the bones and joints in the legs to bear the whole body weight and causing the leg muscles to contract more as they try to maintain balance. This stimulates activity of bone cells (osteoblasts) and the compression on the bones increases the process of mineralization of the bones.[2-4] Muscle contraction is a major force that have great influence on bone mineralization. The effects of exercise on the bones is assessed in terms of physical strain such as the weight of the ground against the body standing on it, i.e. ground-reaction force, or muscle contraction forces on a particular area of bone.[5,6] Weight bearing activity is essential for normal development and maintenance of bone health.[7] Even though swimming is not a weight bearing activity, Derman and colleagues found that swimmers have a higher bone mineral density compared to the control group. It is believed that the main reason for this is that they usually exercise with small weights and a lot of repetition, which may be sufficient stimuli to increase bone metabolism.[8]

There is a close relationship between metabolic bone markers and bone mineral density (BMD); for example, osteocalcin is significantly correlated with BMD in postmenopausal women with osteoporosis.[9] Among the metabolic bone markers, C-terminal telopeptide of type 1 collagen (CTX) is shown to be more sensitive and more specific to bone resorption than other conventional measurements, such as urinary hydroxyproline and urinary calcium excretion.[10] Besides, bone turnover markers can be indirectly used to detect or to monitor the early responses of the skeleton to weight-bearing exercise.[11,12] Biochemical markers are very sensitive to physical activity: their progressive increase occurs 30 minutes from the beginning of exercise (up to 45-50%).[13]

Body mass index (BMI) is a parameter that determines the health risk. Specifically, correlation between BMI and the onset of osteoporosis has been the subject of many studies. For example, Coin and colleagues came to the conclusion that the values of BMI<22 in young adults may carry a higher risk of the onset of osteoporosis in older age, especially in women.14 Hence, literature suggests that it is likely that higher BMI has a positive effect on bones (and therefore reduced risk toward osteoporosis).[14,15] To our knowledge the effect of structured aerobic exercise on bone markers and specifically their relation to BMI (and therefore osteoporosis) in young adults is still not fully understood. According to the position stand on bone health and physical activity of the American College of Sports Medicine (ACSM), moderate-to-high intensity, weight-bearing endurance activities are recommended to help preserve or to increase BMD in adults.1 The level of BMD in later life is a function of the maximum bone mass attained in early adulthood and of subsequent age-related bone loss, which starts in the fourth decade of life and accelerates in early postmenopausal years in women.[16-18] De Jong and colleagues sugested that aerobic physical activity is associated with an increase in BMD in a population with an increased risk for osteoporosis.[19]

Aim of the Study

Given the potential benefit of physical activity to bone markers and BMI our aim is to:

1. Determine the effect of aerobic physical activity on bone metabolism markers: osteocalcin (OC), the bone formation marker, C-terminal telopeptide of type 1 collagen (CTX), the bone resorption marker, in young women

2. Investigate correlation of OC, CTX and BMI in young women engaged into structured aerobic excercise

Material and methods

Current study included 64 healthy young women, aged 19 to 25 years, divided into two groups: intervention group (n=32) and control group (n=32). All participant were not involved in any kind of physical activity before entering the study. The research protocol followed the principles of the Declaration of Helsinki regarding biomedical research involving human subjects. All participants provided written consent subsequent to being informed about the research process.

The study duration was six weeks with follow-up period of four weeks. Intervention group underwent 6-week aerobic physical activity. The aerobic exercise program was consisted of 45 min supervised aerobic exercise sessions two times a week. The supervision and exercise guidance was done by highly skilled professional in physical education and sport. The program consisted of:

- step aerobics for ten minutes
- easy running for five minute
- exercises for the shoulders, arms and legs (in the

form of squats) - a total duration of fifteen minutes

- exercises for the abdominal and gluteal musculature - ten minutes
- a relaxation exercise - five minutes.

While the subjects in the intervention group underwent aerobic physical activity program for six weeks, the subjects in the control group did not receive such program. Blood samples for osteocalcin (OC) and C-terminal telopeptide of type 1 collagen (CTX) were taken at 8 a.m. and analyzed by ECLIA immunoassay method on Roche Elecsys 2010. Body weight and height are measured in the morning as well. BMI was calculated by applying the Quetelét equation: the division of weight (kg) by height (m) squared. Normal BMI for adults is 18.5 to 24.9 kg/m2, persons with BMI below 18.5 kg/m2 are underweight, above 25.0 kg/m2 are overweight.20 Both groups were assessed at baseline, after 6 weeks and after 4-week follow up (only intervention group). Purpose of the follow up period for the intervention group was to investigate long term effects of aerobic physical activity on bone metabolism markers (OC and CTX).

Osteocalcin level in the intervention group was statistically significantly higher after 6-week program compare to the baseline ($p<0.001$), and after 4-week follow up compare to the baseline ($p=0.005$). In the control group, there was no significant difference in osteocalcin level ($p=0.952$).

The collected data were analyzed by statistical analysis by SPSS 17.0.1 (SPSS Inc., Chicago, IL, USA), and statistical significance was set as $p<0.05$.

Results

At baseline there was no observable difference in age, BMI and bone metabolism markers between intervention (IG) and control group (CG) (Table 1).

Table 1. Age and BMI at baseline both intervention (IG) and control group (CG) (n=64)

	IG (n=32)		CG (n=32)		p
	Median	IQR	Median	IQR	
Age	20	(20-21)	20	(20-21)	0.338
BMI (kg/m^2)	21	(20-23)	21	(20-23)	0.868

** Values are presented as median and interquartile range (IQR)*
n – number of subjects

The statistical analysis showed that the level of CTX in the intervention group was not statistically significantly different ($p=0.243$) in all tree measurements, nor in the control ($p=0.264$) in two measurement (Table 2).

Table 2. OC and CTX in intervention (three measurements) and control group (two measurements)

	OC (ng/ml)				CTX (ng/ml)			
	IG M(SD)	p	CG M(SD)	p	IG M(SD)	p	CG M(SD)	p
Baseline	30.2 (7.57)	<0.001*	32.1 (9.52)	0.952	0.52 (0.16)	0.243	0.52 (0.156)	0.264
After 6-week program	34.3 (10.01)		32.0 (7.73)		0.56 (0.20)		0.55 (0.191)	
After 4-week follow-up	32.5 (7.50)	0.005**			0.54 (0.19)			

Values are presented as mean (M) and standard deviation (SD)
**Statistically significant difference of OC level at the baseline and after 6-week program*
***Statistically significant difference of OC level at the baseline and after 4-week follow up*

For underweight subjects (BMI<18.5 kg/m²) of intervention group there was no statistically significant difference in the level of osteocalcin in all three measurements (p=0.903), as well as in overweight (BMI>25 kg/m2) subjects (p=0.067). There is, however, significant increase of OC after the 6-week aerobic program in subjects with normal BMI (p<0.001). Conducted mixed analysis of variance (within groups and between groups) showed that there was no statistically significant interaction of time of measurement and body mass index on the value of CTX (p=0.360) (Table 3).

Table 3. OC and CTX level compare to BMI in intervention group

	OC (ng/ml)				CTX (ng/ml)			
	Baseline	After 6-week program	After 4-week follow-up	p	Baseline	After 6-week program	After 4-week follow-up	p
	M(SD)	M(SD)	M(SD)		M(SD)	M(SD)	M(SD)	
Under weight	25.1 (5.15)	25.2 (7.96)	25.8 (6.56)	0.903	0.4 (0.19)	0.4 (0.25)	0.4 (0.23)	0.360
Normal weight	31.5 (7.96)	37.6 (9.0)	34.5 (6.95)	<0.001*	0.6 (0.15)	0.6 (0.18)	0.6 (0.18)	
Over weight	29.8 (5.35)	26.6 (5.26)	30.8 (6.92)	0.067	0.4 (0.08)	0.5 (0.19)	0.5 (0.18)	

Values are presented as mean (M) and standard deviation (SD)
** Statistically significant difference of OC level in subjects with normal BMI*

Discussion

It is well known that a young bone adapts better to mechanical stress and physical activity than a mature bone. This means that exercising in early childhood is an important factor in prevention of osteoporosis later in life.7 Peak bone mass is achieved by age 30.[21] Due to these reasons, for our study we chose women between 19 and 25 years old. We wanted to investigate how changes in bone metabolism occur at this age, as well as the dynamics of these changes.

Theoretically, the duration of the human bone-remodeling cycle takes about 4–6 months, and the durations of resorption and formation are not evenly divided. The osteoclastic resorption activity (at a specific site) accounted for 3–6 weeks, followed by osteoblast-mediated bone formation, which accounted for 5–9 weeks. Hence, a 6-week exercise program is more feasible than a long-term exercise program (e.g., 20–30 weeks) to investigate bone turnover markers rather than bone mineral accumulation.[22] Based on the concept of bone metabolism, bone health can be estimated via biochemical markers of bone turnover other than densitometric indices.[23]

The results of the current study showed that the 6-week aerobic program increased level of OC, therefore it had the great impact on bone formation, while the level of CTX did not changed, suggesting that program had no influence on bone resorption. The value of OC after one month of relative resting was higher than at the baseline. This suggests a protective effect of physical activity holds also after the completion of exercising.

The results of previous studies on bone turnover and exercise have been inconsistent.[24,25] In a study of mice, results showed significant negative effects on serum CTX (exercise caused a quick reduction in bone turnover). Similar results were demonstrated by Klentrou and colleagues.[25] After 12 weeks of exercise, bone resorption marker, N-telopeptide of type I collagen (NTX), decreased by 14.5 % in the intervention group, while there were no significant changes in the osteocalcin levels.[25] Similarly, in the Wen's study, the changes in the serum CTX levels were significantly different between groups after a 10-week step aerobic exercise; the intervention group showed a trend in down regulating bone resorption activity, which was reflected by a reduction of CTX.[22] This is positively benefited to bone formation. The serum CTX level, was in a declining trend after the 10-

week step aerobic exercise, suggesting that short term exercise program may likely be effective in preventing bone loss and in enhancing bone formation.[22] Similar results were also obtained by Roghani and colleagues, who found increase in bone-specific alkaline phosphates and decrease in NTX after a 6-week, moderate-intensity (50–60 % HER) aerobic (walking on a treadmill) exercise in postmenopausal women with osteoporosis.[26] However, the findings of Phoosuwan, Kritpet and Yuktanandana[27] were inconsistent with those of Roghani et al.. The study showed reductions in both NTX and bone-specific alkaline phosphatase after a 12-week, weight-bearing yoga training program. These mixed down regulations of bone turnover might be due to disparities in exercise mode and intensity.[22,26,27]

Adami and colleagues conducted a study that included eumenorrheic women aged 39 to 45 years, without cardiovascular diseases, fractures and other chronic diseases. The intervention group entered 4-weeks exercise program with continuously increasing intensity of exercise. In the intervention group was found a significant increase of 25% in bone formation markers OC and N-terminal propeptide of procollagen I (PINP) compared with the control group.[28] Those results are consistent with results of current study. In Adami's study[28] there was no statistically significant change in serum CTX, nor was in ours.

Mullins and Sinning, however, showed that 12 weeks of resistance exercise for 18 to 30 years old women, lead to a reduction in BAP as a marker of bone formation, whereas osteocalcin was not significantly changed (contrary to our results). Deoxypyridinoline (DPD), bone resorption marker, rose to a higher level than normal.[29] Results similar to ours are demonstrated with study of Jürimäe and colleagues in which OC in rowers, who were preparing for the competition, was increased, whereas the other markers were not significantly changed.[30]

In current study the biggest impact of the physical activity on bone metabolism, specifically values of OC, occurred in young women with normal body mass index. In other words, current study has shown that the best effects of physical activity on bone can be expected in women with normal BMI. A similar results had Cui and colleagues[15], suggesting that a normal BMI can be protective factor against osteoporosis. While other studies showed negative correlation between osteocalcin and BMI,[31-33] even that obese women had lower prevalence of osteopenia and osteoporosis compared to normal weight subjects.[31]

Conclusion

This research showed that aerobic physical activity increases level of osteocalcin, suggesting that it has positive influence on bone formation in young women, primarily in women with normal BMI. This results could be used as a framework for making program for osteoporosis prevention.

Current study had some limits that need to be mentioned. This was a short-term intervention study that focused on the changes of bone metabolic markers. In the future study should consider longer follow up period, to evaluate time frame of OC protective effect. The study should include measurement of BMD and analyze others bone metabolism markers, such as sclerostin, which is a protein that acts as an inhibitor of bone formation.[34]

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Markeri metabolizma kosti i njihova korelacija sa indeksom tjelesne mase u aerobnoj fizičkoj aktivnosti

SAŽETAK

Uvod: Marker formiranja kosti osteocalcin (OC) i marker resorpcije kosti C-terminalni telopeptid kolagena tipa 1 (CTX) se mogu koristiti za određivanje i praćenje ranog odgovora kosti na fizičku aktivnost. Podaci iz literature pokazuju da veći indeks tjelesne mase (body mass index – BMI) ima pozitivni efekat na kost i može da odloži nastanak osteoporoze.

Cilj rada: Cilj ovog sitraživanja je:
1. Utvrditi efekat aerobne fizičke aktivnosti na OC i CTX kod mladih žena
2. Ispitati povezanost OC, CTX i BMI kod mladih žena uključenih u program aerbne fizičke aktivnosti

Materijali i metode: Istraživanje je obuhvatalo 64 zdrave mlade žene starosti od 19 do 25 godina, koje su podijeljene u dvije grupe: eksperimentalnu (n=32) i kontrolnu (n=32) grupu. Istraživanje je trajalo šest nedjelja uz period praćenja u trajanju od 4 nedjelje. Eksperimentalna grupa je bila uključena u program strukturisane aerobne fizičke aktivnosti u trajanju od šest nedjelja, a kontrolna grupa nije imala fizičku aktivnost u tom periodu. Mjerene su vrijednosti OC, CTX i BMI na početku, nakon šest nedjelja pomenutog programa i nakon četiri nedjelje od završetka programa (samo eksperimentalna grupa).

Rezultati: Postoji statistički značajno povećanje vrijednosti OC nakon šestonedjeljne aerobne fizičke aktivnosti, dok se vrijednost CTX nije značajno promijenila. Maksimalna vrijednost OC je bila neposredno po završetku programa kod učesnica sa normalnim BMI ($p<0,001$). Nije bilo statistički značajne interakcije BMI i vrijednosti CTX.

Zaključak: Aerobna fizička aktivnost povećava nivo osteokalcina, što ukazuje na pozitivan uticaj na formiranje kosti kod mladih žena, naročito kod žena sa normalnim BMI.

Ključne riječi: osteocalcin, C-terminalni telopeptid kolagena tipa 1, metabolizam kosti, aerobna fizička aktivnost

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Importance of Selection a Method of Reconstruction of Digestive Continuity After Gastrectomy

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ABSTRACT

Introduction: Gastrectomy is one of the most common surgical methods for the treatment of gastric cancer, which basically destroys the mechanism and digestion chemistry. Reconstruction after gastrectomy attempts to optimize the antireflux and nutritive component of the postgastrectomic syndrome.

Objective: To determine which reconstructive method after gastrectomy has the optimal synthesis of antireflux and nutritional components.

Patients and Methods: 111 patients were treated for gastric malignancies at the Surgical Clinic of the University Clinical Center in Banja Luka, which were operated with the intention of achieving curability.

Results: Based on Fisher's exact probability test there is no statistically significant difference (p> 0.05) in mortality compared to the restoration of digestive continuity after gastrectomy. Reflux oesophagitis is the dominant modality of morbidity in omega-loop reconstruction (p <0.05). There is no statistically significant difference (p> 0.05) in late dumping syndrome in patients relative to individual gastric substitution options. In the Hunt-Lawrence-Rodino pouch reconstruction option, there is no statistically significant difference (p> 0.05) in the participation of individual modalities of meal quantity in relation to the condition before the disease or the modality of the nutritional status. .

Conclusion: The results indicate the antireflux component of reconstruction Roux en Y and the advantage of the nutritive component in the loop modification (the creation of the Hunt-Lawrence-Rodino pouch).

Key words: gastric cancer, gastrectomy, methods of reconstruction, postoperative morbidity

(Scr Med 2018:49:99-104)

Introduction

Stomach cancer is one of the common visceral neoplasms around the world although with decreasing trend. As gastric malignant surgery is a highly mutilatory operative procedure that substantially changes the mechanism of digestion, the need for finding a modality of digestive tube reconstruction has been imposed which will replacement is the most optimal. Correction of the damaged mechanical component of the digestion is in the focus of the surgeon's interest, while humoral and neural alterations are in the domain of interest of endocrinologists and gastroenterologists.[1-7]

Objective

To determine whether the construction of the gastric reservoir increases the rate of mortality and morbidity operated by gastric malignancies and assess whether the construction of the gastric reservoir has a satisfactory antireflux and nutritional component.

Patients an Methods

The base of the study is represented by 211 patients who have been operated for stomach malignancies at the Clinical Center Banja Luka in the period from 2002 to 2012 and monitored for 5 years after surgery, and the subject of a detailed analysis is 111 patients who were operated with the intention of achieving curability. The quality of life was tested 6, 12, 24 and 60 months after surgery. The paper used the documentation of the Surgical Clinic, the Oncology Clinic, and the Pathology Institute of the Clinical Center in Banja Luka. Classification of patients was done on the basis of sex and age, and malignancies of the stomach based on macroscopic and microscopic appearance, tumor location and stage of the disease. Men were 64 or 57.7%, and women 47 or 42.3%. The lifespan was 60-70 years (36%), adenocarcinoma was 92%, lymphoma 5% and sarcoma 3%. Limited extensibility options were 5%, 43% of subtotal resections, 46% of total gastrectomy and 6% of extensive total gastrectomy were done. In 52.63% of gastrectomed patients, the reconstruction was done with the RY method, 43.86% was made with a gastric reservoir (HLR), and in 2 patients (3.51%), a reconstruction of the omega loop was performed.

Results

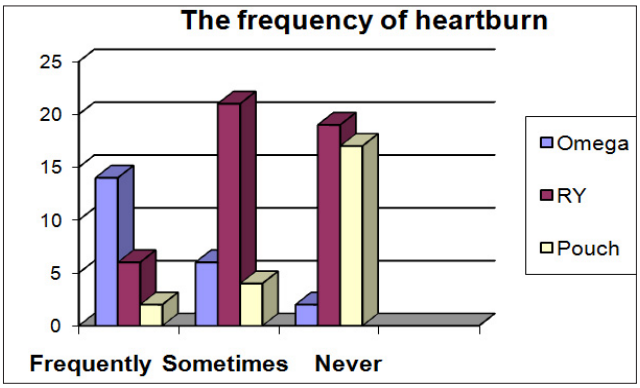
1. Mortality

Postoperative mortality was tested (30 days after surgery). From 111 operated with the intention of achieving radical surgery six patients died (5.41%); one patient with reconstruction omega loop, two patients with RY reconstruction and three with reconstruction HLR reservoir. Based on the Fisher's exact test probability ($p = 0.295$), there was no statistically significant difference ($p > 0.05$) in mortality compared to the option of restoration of digestive continuity after gastrectomy.

2. The frequency of heartburn

Medical history was tested operated on the basis of the survey questionnaire within the Index of quality of life by Eypasch, Williams and Troidl-in of the 36 questions (Gastrointestinal Quality of Life Index- GIQLI).

Chart 1. The frequency of heartburn



Based on the calculated value of the test of the assumed proportions for the option of reconstructing the omega loop ($z = 2.659$; $p = 0.0078$), there was a statistically significant difference ($p < 0.01$) in the participation of patients who had frequent heartburn. With the Roux en Y reconstruction option ($\chi^2 = 8.652$; $p = 0.0132$), there is a statistically significant difference ($p < 0.05$) in the participation of patients who have sometimes had a heartburn. In the Hunt-Lawrence-Rodino pouch reconstruction option ($z = 5.223$; $p = 0.0000$) there is a statistically significant difference ($p < 0.01$) in the participation of a group of patients who have never had a heartburn. (Chart 1).

3. Reflux gastritis and oesophagitis

Endoscopic diagnosis was performed after 6 and 12 months of operation. Based on the calculated value of Fischer's test (Fischer: $p = 0.030$), in the total sample analyzed, there is a statistically significant difference ($p < 0.05$) in the occurrence of reflux gastritis and oesophagitis in patients with respect to certain gastric substitution options, with dominant modality reflux I degree. Among the different modes of reflux, the II and III degrees of reflux are significant in the reconstruction of omega-loop.

4. Dumping syndrome

Dumping syndrome is manifested by vasomotor symptoms, such as: diarrhoea, weakness, trembling, cold sweating, palpitations. Early dumping can be manifested by gastrointestinal symptoms, such as: feeling fullness in the abdomen, abdominal pain, torment, vomiting and explosive diarrhea. We tested an early dumping syndrome (by glucose-Sigstad test) and most patients did not show signs of a serious dumping syndrome.

Based on the calculated value of X^2 test (X^2 = 1.000; p = 0.9098), based on the formed contingency table, there is no statistically significant difference in the total sample (p> 0.05) in early dumping syndrome in patients compared to individual gastric substitution options.

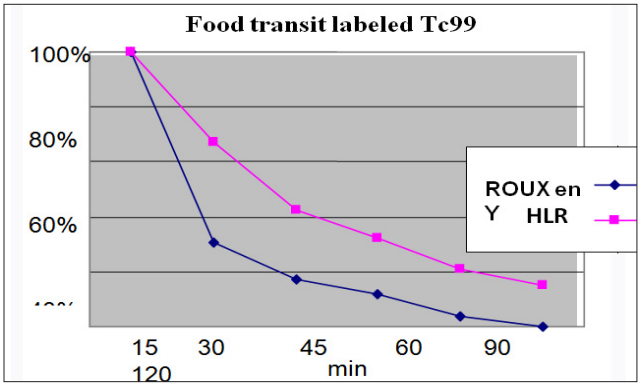
5. Quantity of meals

The quantity of the meal was tested with a questionnaire on the quantity of meals in relation to the condition before the disease (the same, less, much less). There is a statistically significant difference (p <0.05) in the option of reconstruction of the omega loop (X^2 = 9.091; p = 0.0106) in the participation of individual modality of the quantity of meals, with the dominance of those patients who take quantitatively smaller rations compared to the condition before the onset of the disease. In the case of the reconstruction option Roux en Y (z = 5.032; p = 0.0000) there is a statistically significant difference (p <0.01) in the participation of individual modalities of meal quantity, with the dominance of those who take quantitatively much smaller rations compared to the condition before the onset of the disease. There is no statistically significant difference (p> 0.05) in the case of the reconstruction of the Hunt-Lawrence-Rodino pouch (X^2 = 3.217; p = 0.2002) in the participation of individual modalities of meal quantity in relation to the condition before the disease.

6. Food Transit

The food transit was made on a gamma camera using radiofarm (isotope) Tc99m –sulphur colloid in a dose of 2-3 mCi (74-111 kBq). A comparison was made between the RY reconstruction and reconstruction options Hunt-Lawrence-Rodino pouch. With the Roux en Y method, rapid discharge of foods labeled with radioactive Tc99 was registered. After 30 minutes, only about 30% of the total amount of food was registered in the Roux loop region, after about 45 minutes, about 18%, and after 60 minutes, signs of radioactivity (about 10%) were barely displayed. When reconstructing the HLR reservoir after 30 minutes, over 60% of the total amount of food is registered in the reservoir, and after about 60 minutes about 35%. And after two hours, the artifical stomach showed signs of radioactivity (about 10% of the total volume) (Chart 2).

Chart 2. Food Transit



7. Malnutrition

Under moderate malnutrition, a loss of up to 5 kg of preoperative body weight is assumed, medium severe malnutrition, a loss of 5-10 kg of body weight is implied, and loss of more than 10 kg of preoperative body weight is considered to be severe malnutrition. There is no statistically significant difference (p> 0.05) in the involvement of individual modalities of malnutrition in the omega-reconstruction option (X^2 = 0.400; p = 0.8187). In the case of the reconstruction option Roux en Y (X^2 = 18.059; p = 0.0001) there is a statistically significant difference (p <0.01) in the interaction between particular modalities of malnutrition, with the dominant mode of moderate malnutrition. There is no statistically significant difference (p> 0.05) in the participation of individual modalities of malnutrition in the case of the reconstruction of digestion continuity Hunt-Lawrence-Rodino pouch (z = 0.000; p = 1.0000).

8. Nutritional status - (Blackburn)

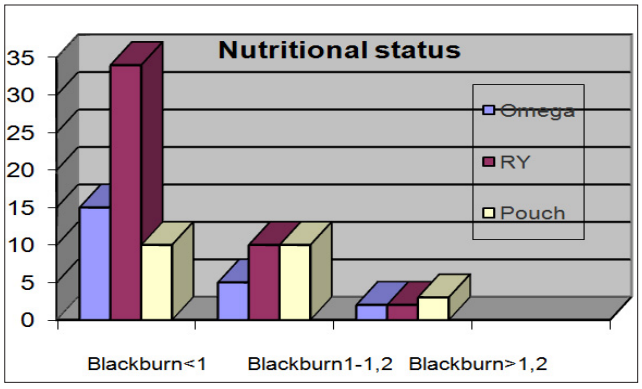
The relationship between current and preoperative body weight (Blackburn) served to evaluate the postoperative nutritional status of the patient. It was used in the following way:

1. Blackburn <1 ---- malnutrition;
2. Blackburn 1-1.2 - optimum nutrition;
3. Blackburn> 1,2 - adiposity.

Based on the calculated value of the test of the assumed proportions for the omega loop reconstruction option (z = 3.662; p = 0.0003), there is a statistically significant difference (p <0.01) in the participation of the Blackburn

nutritional status modality <1. In the case of the reconstruction option Roux en Y (z = 7.388; p = 0.0000) there is a statistically significant difference (p <0.01) in the participation of the Blackburn nutritional status modality <1. At Hunt-Lawrence-Rodino pouch reconstruction (z = 1.262; p = 0.2069) there is no statistically significant difference (p> 0.05) in the participation of certain modalities of nutritive status (Chart 3).

Chart 3. Nutritional status - (Blackburn)



Discussion

Extensive surgery of visceral malignancy, as well as various modalities of oncological treatment, have prolonged the lifespan of the patients. As certain options of gastrointestinal continuity reconstruction have a different effect on the reduction of the intensity of postgastrectomy sequela, the problem of the importance of selecting digestive reconstruction after the surgical treatment of gastric malignancies has been imposed. The dominant sequences of postgastrectomy syndrome are, of course, alkaline reflux and nutritional deficiency. The incidence of heartburn was dominant in the omega loop option, while in the reconstruction of the reservoir they were registered in one-fifth of the patients. Reflux gastritis and oesophagitis is a sequela that is registered in 28.3% of the operatives, and this is dominant in the option of reconstructing the digestive tract with omega-loop. The late dumping syndrome was registered in 24,17% of the observed, dominant total gastrectomy. There was no statistically significant difference in relation to individual methods of reconstruction. Early dumping syndrome was tested according to Sigstad (a glucose load test) and was recorded in one third of the patients. Serious problems are registered predominantly in total gastrectomy, and among some reconstructive options, the occurrence of moderate and mild problems in the method of reconstruction by omega loop is more frequent. In several series analyzing the quality of life after gastric replacement, the authors find the highest incidence of heartburn after reconstruction without a reservoir, which is confirmed by the endoscopic finding of reflux oesophagitis. A similar finding was found in the quantification of the severity of the postprandial dumping syndrome with the dominant symptomatics in patients who underwent reconstruction without a reservoir. The frequency of daily food rations was greatest in gastric replacement options with the Hunt-Lawrence-Rodine reservoir, and the quantity of meals was slightly higher in the same option for the reconstruction of digestive continuity (Hunt-Lawrence-Rodino). Nutritional status was assessed based on the current and optimal weight ratio (Blackburn) and the best result was registered with the reconstruction option with the reservoir. Visick grade, Karnofsky index of general physical abilities, Spitzer index, Troidl scoring system parameters were used which indicate optimal postoperative results achieved by creation of a gastric reservoir that has antireflux and nutritive component.[1-6]

Analyzing the quality of life after some options of surgical reconstruction of digestive continuity, data on postoperative malnutrition caused by a loss of body weight over 5 kg in the three-month period are predominant after total gastrectomy and gastric substitution with the reservoir. Analyzing dietary restrictions that lead to weight loss, it can be concluded that there is no statistically significant difference in nutritional value after 3, 6, and 12 months in some modes of digestive continuity reconstruction.[7-10]

In several series, authors evaluate the quality of life for certain gastric substitution options and come up with similar results: patients with omega-loop (Brown) had a heartburn, and endoscopically confirmed reflux esophagitis stage I or II. In a patient in whom a conversion of omega loop was performed in the antireflux Roux en Y option (Schloffer reconstruction), a complete remission of the disorder occurred. After reoperation, patients achieved approximately preoperative body weight. The authors conclude that total gastrectomy should not be avoided because of the fear of developing postoperative progressive malnutrition. A simple Roux en Y option without a reservoir design is a satisfactory option for reconstructing the digestive tract after gastrectomy, and the issue of creating an artificial reservoir remains open. Creation of omega loop does not prevent the occurrence of reflux oesophagitis and should be avoided. The Cuschier scoring system points to the simple Roux en Y option and Roux en Y with the reservoir (Hunt-Lawrence-Rodino) as the optimal nutritional and antireflux options for gastric replacement.[11-16]

In the analyzed sample of patients undergoing surgery,

compared to the frequency of daily meals tested after 6, 12, 24, 60 months after surgery, there is a significant difference in individual reconstruction options. The method of reconstruction of the reservoir is dominated by the participation of the modalities of less than 4 meals a day, and with Roux en Y reconstructive methods the modality of more than 6 meals a day is most present. The quantity of the largest meal was taken by patients in whom the reconstruction of the reservoir was done, where one third gave data about approximately the same amount of foods for each meal as before the operation. After 30 minutes, only about 30% of all foods were registered in Roux loop, after about 45 minutes, about 18%, and after about 60 minutes about 10%. When reconstructing the reservoir, after 30 minutes over 60% of the total amount of food is registered in the reservoir, and after 60 minutes about 35%. And after two hours, the artifical stomach showed signs of radioactivity (about 10% of the total volume). Comparing the rate of discharge of food from the artificial gaster (gastric pouch) and simple Roux en Y reconstruction methods, the authors have come up with results that show that Roux en Y methods were the rapid discharge of foods labeled with radioactive Tc99, which is a common cause of dumping syndrome and postoperative malnutrition.[17-22]

In the overall sample analyzed, about two-thirds failed to reach preoperative body weight, and statistically significant is the equal participation of all nutritient status modes in the reservoir reconstruction option. The option of gastric substitution by omega loop in a significant percentage causes the occurrence of gastritis and oesophagitis reflux which is the dominant component of the postgastrectomic syndrome. The obtained results of the quality of life assessment are comparable with the results of other statistical series. They confirm the antireflux component Roux en Y loop and its intestinoplasty and emphasize the advantage of the nutritional component of the loop modification (creations of the pouch).

Conclusion

Reflux of biliopancreatic content adequately prevents Roux en Y loop from the restoration of digestive continuity, but its nutritional component is insufficient. Improvement of the nutritional component Roux en Y reconstruction method can be achieved by intestinoplasty of the drainage (loop modification), but the issue of satisfactory correction of malnutrition remains unresolved. The option of gastric substitution by the reservoir reduces the level of restriction of the food comfort caused by the loss of the stomach as a food reservoir (it allows for the taking of a quantity of meal volume and reduces the daily number of meals), while slowing the transit of food reduces the incidence of the emergence of a dumping syndrome.

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Značaj izbora metode rekonstrukcije digestivnog kontinuiteta nakon gastrektomije

SAŽETAK

Uvod: Gastrektomija je jedna od najčešćih hirurških metoda liječenja karcinoma želuca koja u osnovi narušava mehanizam i hemizam probave. Rekonstrukcijom nakon gastrektomije pokušava se optimizirati antirefluksna i nutritivna komponenta postgastrektomijskog sindroma.

Cilj rada: Utvrditi koja metoda rekonstrukcije nakon gastrektomije ima optimalnu sintezu antirefluksne i nutritivne komponente.

Pacijenti i metode: Analizirano je 111 pacijenata operisanih zbog malignoma želuca na Hirurškoj klinici Univerzitetskog Kliničkog centra u Banjaluci koji su operisani sa namjerom postizanja kurabilnosti.

Rezultati: Na osnovu Fisher-ovog testa egzaktne vjerovatnoće ne postoji statistički značajna razlika ($p>0,05$) u mortalitetu u odnosu na opciju restauracije digestivnog kontinuiteta nakon gastrektomije. Refluks ezofagitis je dominantni modalitet morbiditeta kod rekonstrukcije omega vijugom ($p<0,05$). Nema statistički značajne razlike ($p>0,05$) u kasnom dumping sindromu kod pacijenata u odnosu na pojedine opcije želučane supstitucije. Kod opcije rekonstrukcije Hunt-Lawrence-Rodino pouch ne postoji statistički značajna razlika ($p > 0,05$) u učešću pojedinih modaliteta kvantiteta obroka u odnosu na stanje prije bolesti niti modaliteta nutritivnog statusa.

Zaključak: Rezultati ukazuju na antirefluksnu komponentu rekonstrukcije Roux en Y i prednost nutritivne komponente kod loop modifikacije (kreacije Hunt-Lawrence-Rodino pouch-a).

Ključne riječi: karcinom želuca, gastrektomija, metode rekonstrukcije, postoperativni morbiditet

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Complications of Diabetes Mellitus on Muscles and Joints of Lower Extremities

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ABSTRACT

Introduction: Non-enzymatic protein glycosylation in diabetic patients leads to stiffening of collagen-containing tissues affecting joint mobility. Motor dysfunction in diabetic patients can be detected as muscle weakness or atrophy.

Objective: To determine the presence of muscles weakness and limited joint mobility at ankle (AJ), subtalar (SJ) and first metatarsophalangeal joint (I MTP) in diabetic patients and to determine impact of diabetes duration on those changes.

Patients and Methods: A cross-sectional study was conducted among 100 diabetic patients in "Primary Health Care Centre Banjaluka" in 2014. Function of ten foot and ankle muscles has been evaluated by manual muscle testing. Muscle strength was scored by semiquantitative grading system used in the Michigan Diabetic Neuropathy Score. Range of motion (ROM) at the AJ, SJ and I MTP was measured with goniometer.

Results: The average patients age was 61.91±10.74 and diabetes duration 12.25±8.60 years. The average strength of foot and ankle muscles expressed by muscle score was 11.56±5.08. The average ROM at AJ (47.85°) was significantly decreased compared to the reference value that is 65° (t =-15.378, P=000). The average ROM at SJ (35.10°) was significantly decreased compared to the reference value that is 50° (t =-15.378, P=000). The average ROM at the I MTP (72.70°) was significantly decreased compared to the reference value that is 120° (t =-15.378, P = ,000).

Conclusion: Patients with diabetes have decreased foot and ankle muscle strength, and the average values of the range of motion at AJ, SJ and I MTP, but the duration of the diabetes does not correlate significantly with those changes.

Key words: diabetes, muscle strength, range of motion

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Introduction

Diabetes mellitus (DM), or diabetes is the global epidemic of the 21st century and it is now the fourth leading cause of death in most developed countries.[1] Diabetes complications in the lower extremities are a major cause of morbidity, disability, emotional and physical suffering in people with DM[2] generating at the same time huge economic costs for patients, their families and the entire society.[3] Non-enzymatic glycosylation of the protein caused by long standing hyperglycemic state during longer DM duration leads to stiffening of collagen containing tissues,[4,5,6] which reflects joint structure decreasing elasticity of cartilage, ligaments, and joint capsule.[5-7] A key factor of the tissue damage in patients with DM is gradually and excessive accumulation of advanced glycation end products (AGEs) that produce abnormal covalent cross-links within collagen fibers and other proteins. The most extensive accumulation of AGEs occurs in tissues with low turnover such as cartilage, bone and tendons. Once formed, AGEs can be decomposed only when the protein they are incorporated into is degraded.[8]

Limited joint mobility (LJM) at ankle joint (AJ), subtalar joint (SJ) and first metatarsophalangeal joint (MTP) results in high focal plantar pressures with increased ulceration risk in patients with neuropathy.[4] LJM is often overlooked because it causes small disablement and is thought to have less significant clinical consequences. Determination of the foot and ankle joint mobility is a simple and rather exact test to identify diabetic patients with an at-risk foot and, might be useful as a screening tool in diabetic patients to identify those with an at-risk foot because of its price and simplicity.[6,9]

Motor dysfunction in patients with DM can be detected as muscle weakness as well as atrophy of muscular tissue. It is usually found distally in the extremities, primarily in the lower extremities and is believed to be caused by diabetes neuropathy (DN).[10] Muscle atrophy is closely related to severity of DN. Since DN shows a centripetal pattern of progression, quantification of the more distally situated foot muscles could possibly serve as an early marker for motor dysfunction in DN.[11] Although muscular weakness has an important role in losing independence and impairing the quality of life, it represents neglected complication of long-term DM.[12] Muscle strength reduction is most commonly associated with the presence of DN,[10,13,14] but studies have shown the existence of muscular weakness in patients without neuropathy, suggesting the existence of other mechanisms that affect it.[7] The association among ROM, muscle strength and function loss can lead to altered foot rollover during gait, as their integrity is needed to enable proper load absorption.[5] Elevated plantar pressure coupled with a longer period of time spent in support phase in DN patients contributes to the susceptibility for skin damage through a prolonged mechanical load on tissue leading to skin breakdown and ulceration.[15]

Keeping in mind serious consequences that complications of DM in the lower extremities make on a personal and social level, inevitably raises the question what can be done to reduce their rate and severity. The implementation of strategies that include education, multidisciplinary treatment of foot ulcers and close monitoring, can reduce the rate of diabetic amputations between 49% and 85%.[4,16-18] Proper metabolic control of both types of DM may delay the onset and progression of diabetic complications.[19]

Objective

To determine the presence of the foot and ankle muscles weakness and limited joint mobility at the AJ, SJ and first MTP in people with diabetes and to determine the impact of the diabetes duration on those changes.

Patients and Methods

A cross-sectional study was conducted among 100 diabetic patients (both type DM) who are registered with family physicians in the "Primary Healthcare Centre Banja Luka" during 2014. The sample was formed in a way that the patients who approached family doctor for a prescription for insulin or oral antidiabetic drugs in 10 family medicine ambulances were over the time successively asked to enter the study. The survey included: the review of medical records, history-taking, measurement and testing. The study was approved by the local ethics committee and informed consent was obtained from patients.

Medical records were source of personal data, data on DM - type, therapy and HbA1c value not older than 6 months. History-taking data were entered in the anamnestic list, and include information about duration and treatment of DM.[20,21] The clinical examinations of muscles and joints were performed routinely by the same examiner.

Muscle function of the foot and ankle muscles has been evaluated by manual muscle testing (MMT) on the dominant leg. MMT means assessing ability of the muscle to produce active movement against the examiner's resistance. Muscle strength (i.e., weakness) was scored using a semiquantitative grading system that was based on the scoring system as used in the Michigan Diabetic Neuropathy Score.[5,22,23] Muscle weakness was scored as 0 for normal muscle strength, 1 for mild, 2 for severe weakness, and 3 for complete loss of strength.

A muscle score (MS) was, therefore, obtained for each set of muscles examined. Higher values for this score represented increased muscle weakness.[22,24] In the positions described for manually clinical assessment[25] the function of the following muscles was evaluated: triceps surae, tibialis anterior, interosseus, lumbrical, flexor hallucis brevis, extensor digitorum brevis, extensor digitorum longus, flexor digitorum brevis, extesnosor hallucis longus and extensor hallucis brevis.[5]

Joint mobility at the AJ, SJ and first MTP was measured with a goniometer on the dominant lower limb. At the AJ range of motion (ROM) was measured with the patient supine and goniometer set with immobile prong in line with calf, mobile prong in line with external edge of the foot and center of goniometer above the joint center. The maximum range of active talar flexion and extension was measured and the sum of the values was recorded as ROM at the AJ. At the SJ ROM was measured with the patient pronate; a vertical line was marked on the patient's skin from heel to midcalf; goniometer set with immobile prong in line with the line on the calf, mobile prong in line with the line on the heel and center of goniometer above the joint center; the maximum range of calcaneal active inversion and eversion were measured with a goniometer and the sum of the values was recorded as ROM at the SJ. At the first MTP range of active extension to plantar flexion was measured with the patient in the supine position; horizontal line was drawn from the first toe to the heel in line with medial edge of the foot; goniometer center set above the joint center, immobile prong in line with proximal part of drawn line and mobile prong in line with the distal part of the line; the sum of maximal extension and flexion was recorded as ROM at first MTP joint.[26,27] As a reference value of ROM is considered a sum of the minimal normal values of the movement amplitude cited in relevant literature.[28]

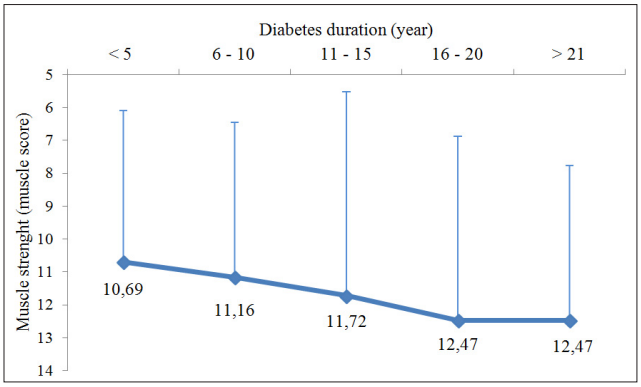
The statistical analyses were done using the software package "IBM SPSS Statistics". To test the statistical significance between variables the ANOVA and the Student's t test were applied. The cut off for the results significance was $p<0.05$.

Results

There were more women (53%) than men (47%) in the study group. The average age of the patients was 61.91± 10.74 years. The majority of patients (94%) had DM type 2 while type 1 DM had 6% of them. The average duration of diabetes was 12.25± 8.60 years. In the study group 86% of patients had HbA1C test result not older than 6 months, while 14% of patients did not have it. The average value of HbA1C in the study group was 7.85%±1.73. The even number of patients was treated with insulin and oral antidiabetic drugs (46% each), and combined oral and parenteral therapy had 8% of the patients. The average muscle strength of the foot and ankle muscles expressed by MS was 11.56±5.08. The duration of the DM and muscle strength were not significantly correlated (r =1.41, p = .160).

Relation between the muscle strength and duration of the DM is shown in Chart 1. The muscle strength was below the average value in patients with a duration of DM more than 11 years, whereas the muscle strength was above average or closely average value in patients with a duration of DM below ten years. With the increased duration of the DM muscle strength tends to decrease, but this difference was not statistically significant (F=0.583, p=677).

Chart 1. Correlation of diabetes duration and muscle strength expressed by muscle score (n=100)



Study results of the ROM at AJ, SJ and I MTP in patients with DM are shown in Table 1.

Table 1. Results of measurement of the active mobility at ankle joint, subtalar joint and first metatarsophalangeal joint in diabetic patients (n=100)

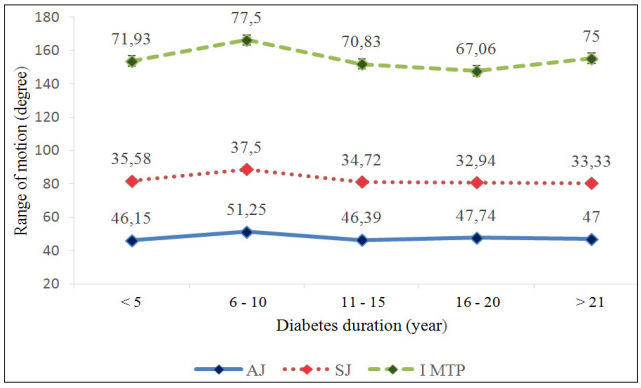
	Average value of the ROM	Reference value of the ROM*	p
AJ mobility (°)	47.85±11.2	70	.000
SJ mobility (°)	35.10±8.7	50	.000
I MTP mobility (°)	72.20±21.1	115	.000

AT – ankle joint, SJ – subtalar joint, I MTP – first metatarsophalangeal joint;

The average ROM at AJ was 47.85° and was statistically significantly decreased compared to the reference value that is 65° (t =-15.378, P=000). The average ROM at SJ measured in examined patients was 35.10° and it was

statistically significantly decreased compared to the reference value that is 50° (t =-15.378, P =000). The average ROM at the first MTP joint in the study group was 72.70 ° and it was statistically significantly decreased compared to the reference value that is 120° (t =-15.378, P=000). The duration of diabetes has not influenced significantly the mobility at the AJ (F=0.8008, p=0.5276), the SJ (F=0.8965, p=0.4693) and the first MTP joint (F=0.6942, p=0.5977) as shown in Chart 2.

Chart 2. The influence of the diabetes duration on the range of motion at ankle joint, subtalar joint and first metatarsophalangeal joint in diabetic patients (n=100)



AT – ankle joint, SJ – subtalar joint, I MTP – first metatarsophalangeal joint.

Discussion

Muscle function of the foot and ankle muscles in this study has been evaluated in ten muscles applying the scoring system as used in the Michigan Diabetic Neuropathy Score. Mean MS of evaluated muscles was 11,56 and represents mild muscle weakness in the study group. Only 13% of patients had preserved muscle strength, 23% of patients had severe muscle weakness, none of them had complete loss of strength, while the most of patients (64%) had mild muscle weakness. Data from this study are consistent with the results of research that has been done by Andersen10[13], Andreassen[14], Giacomozzi[7] and Camargo[29], that have confirmed the existence of a decrease in muscle strength in people with DM, especially in the region of ankle and knee. Van Shie stated that more than 40% of patients with DM had a decreased muscle strength.[22] Muscle quality (power per muscle mass unit) is lower in patients with DM, particularly with the longer duration and poorer control of the disease. Decrease in muscle strength has been found even in people who had impaired glucose tolerance.[10] Ijzerman led the study on the impact of DM and DN on muscle strength, mobility and quality of life. The results of the study shown that DM affects the reduction of muscle strength by 30-50% in the upper and lower extremities, and that loss of strength and decreased mobility reinforce each other by reducing individual, and in particular associated quality of life of patients with diabetes.[30] Loss of muscle strength is an expected consequence of motor nerves damage as a part of neuropathy, while DM affects strength loss by some other factors such as the abnormality of intrinsic muscle, damage in capillary flow, peripheral arterial disease and damage to myofascial structure due to hyperglycemia.[12,29] Balducci has found that the loss of muscle strength is related to the appearance of DN, but also to the other microvascular and macrovascular complications, and the loss of muscle strength in patients with DM is affected by poor transport of blood after the contraction that occurs as a result of damage to the autonomic nerve fibers.[12] Greenman has proven that diabetic patients had diminished oxygen supply to the muscle cells and decreased muscle energy reserves as a result of changes in the microcirculation. He has also found that muscles atrophy in the diabetic foot already existed during the subclinical stage of DN, even before the development of clinical signs of disease.[31] Sawacha demonstrated the presence of changes in the electrical activity of the muscles in the patient with DM which could not be correlated with the presence of DN.[32] Identified early changes in the muscles of patients with DM, but also the all other changes of musculoskeletal system, indicate the need for planning and implementing prevention and rehabilitation programs aimed at reducing all consequences of DM, not only DN.[32,33]

Studies on ROM at AJ, SJ and first MTP joint shown that those three joints were reliable mobility measurement locations.[34] The average values of the ROM at AJ, SJ and first MTP joint in the study group were significantly lower than the reference value of ROM in these joints. Data obtained by conducted study are in compliance with data from the other studies.[35-38] Golsdmith found that the LJM can be found in up to 30% of children with DM type 1, and in up to 45% of adult patients with DM type 2.[37] Somai states that between 30% and 40% of the patients with DM have LJM.[39] Giacomozzi confirmed the existence of LJM in all directions at the AJ and SJ in patients with DM explaining it by changes in the structure that reduce the elasticity of the cartilage and joint capsules.[7] Muelle have found a significant difference in the ROM at AJ and SJ in patients with diabetic ulcer compared with the control group without DM.[35] Rao has confirmed the existence of limited passive dorsiflexion and elasticity at the AJ which it is considered as key factor of the increased plantar pressure in patients with DM.[40]

This study did not confirm the influence of the duration of DM to the RAM at AJ, SJ and first MTP joint. The development of the LJM is complex and multifactorial,

caused by the changes in anatomical structures involving the skin, subcutaneous tissue, muscle, joint capsules, tendons, ligaments and the bone components.[35,39] Accumulation of AGEs due to hyperglycemia is one of the most important factors of the tissue damage in patients with DM.[8,41] The main mechanical effect of AGEs is loss of viscoelasticity of the tissue that occurs due to damaged fiber sliding at the level of extracellular matrix which has potentially important implications for the tissue damage accumulation, mechanically regulated cellular signals and the matrix remodeling.[42]

The tissues damage in diabetic patients causes the alterations in the segmental mobility and affects foot rollover process.[5,6,43] The reduced ankle ROM may interfere in the foot adaptation to changes in foot-floor interaction. Foot rollover process is dependent on the proper mobility of ankle and foot joint to ensure adequate contact of the plantar regions in a progressive temporal order from the heel to the metatarsal heads and hallux during the load phase. The alterations in the foot rollover process will lead to an alterations of loads distribution over the plantar surface and predispose it for ulcer development.[44] Prolonged hyperglycemia causes other structural changes such as the skin thickening, atrophy and impaired muscle activation affecting additionally the physiological gait mechanism.[45]

The goals of physiotherapy in patients with DM are prevention of complications, decrease the effects of immobilization, maintenance of functional capacity and minimizing the presence of the complication.[46] Physiotherapy moderately changes the rollover process of the foot toward the physiological movement in patients with DM and at the same time improves the distribution of a dynamic pressure, torque of the ankle extensors and functionality of the foot and ankle muscles. Specific gait and balance training in combination with functionally oriented strengthening may improve gait and balance, muscle strength, and increase the mobility of joints in patients with DM.[45,47,48] Physical therapy may improve the mobility of ankle and foot joints and thus be useful in the prevention of diabetic ulcer that need to be proven by further research.

Conclusion

Patients with diabetes have decreased foot and ankle muscle strength, and the duration of the diabetes does not correlate significantly to the muscular strength. In patients with DM, the average values of the range of motion at ankle, subtalar joint and first metatarsophalangeal joint are significantly lower compared to the reference value while the duration of diabetes does not correlate significantly with the mobility of the foot and ankle joints.

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Mišićnozglobne komplikacije šećerne bolesti na donjim ekstremitetima

SAŽETAK

Uvod: Hiperglikemijski uslovljena glikozilacija proteina kod oboljelih od dijabetesa dovodi do povećanja rigidnosti svih kolagenskih tkiva što se odražava na pokretljivost zglobova. Motorna disfunkcija kod oboljelih od dijabetesa se prepoznaje kao gubitak mišićne snage ili kao atrofija mišića.

Cilj rada: Utvrditi prisustvo promjena mišićne snage mišića pokretača stopala i prstiju i obima pokreta u gornjem nožnom (GNZ), donjem nožnom (DNZ) i prvom metatarzofalangealnom (I MTP) zglobu kod oboljelih od dijabetesa i utvrditi uticaj trajanja dijabetesa na te promjene.

Ispitanici i metode: Istraživanje je provedeno kao studija presjeka među oboljelima od dijabetesa u „Domu zdravlja u Banjaluci“ 2014. godine. Uzorak je činilo 100 ispitanika. Mišićna snaga je procjenjivanja manuelnim mišićnim testom (MMT) na deset mišića uz primjenu semikvantitativnog bodovnog sistema iz Michigan Diabetic Neuropathy Score-a. Obim pokreta u GNZ, DNZ i I MTP zglobu je mjeren goniometrom.

Rezultati: Prosječna starost ispitanika bila je 61,91±10,74 godina, a prosječno trajanje DM 12,25±8,60 godina. Prosječna snaga mišića pokretača stopala i prstiju izražena skorom mišićne slabosti je bila 11,56±5,08. Prosječna vrijednost obima pokreta u GNZ (47,85°) je bila značajno manja u odnosu na referentnu vrijednost 65° (t=-15,378,p=,000). Prosječna vrijednost obima pokreta u DNZ (35,10°) je bila značajno manja u odnosu na referentnu vrijednost 50° (t=-15,378,p=,000). Prosječna vrijednost obima pokreta u I MTP zglobu (72,70°) je bila značajno manja u odnosu na referentnu vrijednost 120° (t=-15,378,p=,000).

Zaključak: Oboljeli od dijabetesa imaju smanjenu mišićnu snagu mišića pokretača stopala i prstiju i smanjene amplitude pokreta u GNZ, DNZ i I MTP zglobu, ali trajanje dijabetesa ne utiče na te promjene.

Ključne riječi: dijabetes, snaga mišića, obim pokreta.

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The Value Assessment of Clinical Trials Based on Electrophysiologically Verified Lumboischialgia

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ABSTRACT

Introduction: Lumboischialgia is defined as pain in the distribution of ischemic nerve caused by a pathological change in the nerve itself, whereas lumbago is a localized spondylogenic pain that is not followed by a neurological deficit, and is a consequence of muscular bone dysfunction of the lumbosacral region. Previous studies which investigated the value of clinical trials in the diagnosis of lumboischialgia did not find a high sensitivity and specificity in those tests.

Objective: Our objective was to define clinical tests that indicate the existence of radiculopathy and to determine the value of the overall diagnostic finding in relation to the findings of the EMNG examination.

Methods: The sample consisted of 100 patients of both genders, aged 18-65. The inclusive criteria were: strong lower back pain propagating in one of both legs and lasting for 1-3 months and the medical history suggesting a radicula lesion. Non-inclusion criteria were the following: symptoms of cauda equine, acute febrile condition, existence of tumors, vertebral fractures, lesions of central motoneuron, inability to perform the EMNG examination, acute psychotic conditions, operations of the spine and pregnancy. Immediately before each EMNG examination, medical history was taken with defined questions on the existence of pain stronger in the leg than in the spine, dermatome deficit, pain during labor and weakness in the leg.

Results: Patients usually have a total of two (31%) and three (26%) positive clinical signs of lumboischialgia. By statistical analysis, three clinical trials proved to be discriminatory in terms of verification of radiculopathy: positive Lazarevic test, paresis of a particular muscle group, and absence or reduction of the patellar or Achilles reflex. After processing with logistic regression, the statistically predictive value is retained by a positive Lazarevic test. The analysis of the surface under ROC curve shows that the positivity of four or more clinical tests is statistically the best limit value, with a specificity of 67% and a sensitivity of 56%.

Conclusion: The conducted study indicates the statistical significance of the frequency of positive clinical trials: Lazarevic test, objective muscular weakness and absent reflex, in persons with electrophysiologically verified lumboischialgia.

Key words: clinical signs, radiculopathy, electromyoneurography

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Introduction

Ischialgia is defined as pain in the distribution of ischemic nerve caused by a pathological change in the nerve itself. Lumbago implies localized spondylogenic pain not accompanied by neurological deficits and is the consequence of muscular bone dysfunction of the lumbosacral region.[1]

Hippocrates (460-357B.C.) first used the term ischias that comes from the Greek word ischios (hip) in its work "Tractat about Diseases ". Under this name, he implied a pain in the hip joint that spreads from buttocks and neck along the thigh and leg.[2] Laza Lazarević, was a prominent writer of Serbian realism, a doctor, a lawyer and practically the first Serbian neurologist. In his work "Ishias Cotunnii's post "[3,4] he was the first to describe the characteristic sign of the sciatica (from which he himself suffered).

The pain of a radicular character that occurs when lifting the leg is still called Lazarevic's sign. Other clinical cardinal signs of radiculopathy include lower back pain and radiance in the root distribution, often associated with loss of sensitivity and cramps of paravertebral musculature. Motor weakness may also be present. The sensory and motor symptoms of radiculopathy depend on the nerve root or the roots that are damaged. Each nerve root provides a sensation of sensitivity to a specific skin region known as dermatom and motor inertia of certain muscles known as myotoma.

Musculoskeletal reflexes can also show abnormalities in radiculopathy, depending on the damaged nerve root. At the lower extremities, the patella and Achilles reflexes are usually examined. Patelar reflex may be lower in damage to the root of L3, L4, rarely L2. The Achilles reflex is absent and decreased in the root lesion S1. There is no routine reflex for estimating root L5, occasionally a reflex m. tibialis post. and medial hamstrings can be induced. And in case of asymmetry, L5 radiculopathy can be suggested. However, both of these reflexes are often absent in healthy individuals.

EMNG of lower extremities is an objective and highly reliable diagnostic test method for suspected lumbosacral radiculopathy[5,6] and, according to the protocol, it is performed after a clinical examination. The Needle EMG Analysis of electrical activity in the relaxed muscle and during its contraction determines the level of lesion with a specificity of 85%.[7]

Objective

The objective is to examine the degree of compatibility of the clinical finding and objectively electrophysiologically verified lumbosacral radiculopathy through the individual definition of the sensitivity and specificity of clinical trials in relation to the same.

Methods

Basic cohort consisted of 100 patients of both genders, aged 18-65. The inclusive criteria were: strong lower back pain propagating in one of both legs and lasting for 1-3 months and the patient history suggesting a radicula lesion. Non-inclusion criteria were the following: symptoms of cauda equine, acute febrile condition, existence of tumours, vertebral fractures, lesions of central motoneuron, inability to perform nuclear magnetic resonance examination (due to metal objects in the organism, claustrophobia), acute psychotic conditions, inability to perform the EMNG examination (due to the phobia of needles), operations of the spine and pregnancy.

Clinical examination

The clinical examination, by examining the mobility of the lumbosacral spine and leg, the paralumbar muscular tension, the gross motor power of leg segments, sensitivity and muscular tendon reflexes, was performed just prior to electrophysiological examination, which is a common practice.

Electromyoneurography (EMNG)

Electrophysiological confirmation of the existence of the acute polyradiculopathy included the registration of the acute denervation in the investigated muscles and long polyphasic potential in more than 30% of the motor units. In every investigated muscle, 10 different motor units were electrophysiologically studied by estimating the average amplitude, duration and the percentage of polyphasic potential, as well as the degree of regrutation of the voluntary sample.

Analysis of data

Data obtained through conversation and the electrophysiological examination were imported into the pre-defined data in the software Microsoft Excel 2003. It was ascertained that there were no incorrect data and no missing data. The rest of the analysis was performed by the specialised statistical packages of the SPSS 15.0.[17]

Results

Table 1 shows the prevalence in the overall sample of particular clinical signs, such as the Schober sign, Lazarević's sign of the raised leg, the absent reflex, the sensitivity drop, the weakness of the myotoma, and Bell's

sign of the paralumbular musculature.

Table 1. Prevalence of individual clinical signs in the total sample

Sign	N	%
Schober sign	61	61.0
Lazarević sign	57	57.0
Reflex absent	41	41.0
Sensitivity drop	34	34.0
Weakness of myotoma	28	28.0
Bellov sign	26	26.0

The most common clinical signs in the overall sample of patients with a clinical picture of lumbosacral radiculopathy are Schober's sign (61%) and Lazarević's sign (57%). Distribution of the total number of clinical signs in the total sample is shown in Table 2. Patients in the total sample usually have a total of two (31%) and three (26%) positive clinical signs.

Table 2. Distribution of the summed number of clinical signs in the total sample

No. of signs	N	%
0	6	6.0
1	15	15.0
2	31	31.0
3	26	26.0
4	18	18.0
5	4	4.0
6	0	0.0

Patients in the total sample usually have a total of two (31%) and three (26%) positive clinical signs.

Table 3. The absence or reduction of the patellar or Achilles reflex

Sign	Electromyonurographic finding								
	Negative		Positive						
	N	%	N	%	X2	P*	Φ	OR	95% CI
Bellov sign									
Negative	28	(37.8)	46	(62.2)	0.42	0.637	0.06	1.37	(0.53-3.56)
Positive	8	(30.8)	18	(69.2)					
Schober sign									
Negative	11	(28.2)	28	(71.8)	1.69	0.209	-0.13	0.57	(0.24-1.34)
Positive	25	(41.0)	36	(59.0)					
Lazarević sign									
Negative	23	(53.5)	20	(46.5)	10.02	0.003	0.32	3.89	(1.64-9.21)
Positive	13	(22.8)	44	(77.2)					
Sensitivity drop									
Negative	22	(33,3)	44	(66.7)	0.60	0.511	-0.08	0.71	(0.30-1.68)
Positive	14	(41.2)	20	(58.8)					
Reflex absent									
Negative	27	(45,8)	32	(54.2)	5.95	0.020	0.24	3.00	(1.22-7.38)
Positive	9	(22.0)	32	(78.0)					
Weakness of myotoma									
Negative	31	(43,1)	41	(56.9)	5.56	0.021	0.24	3.48	(1.19-10.18)
Positive	5	(17.9)	23	(82.1)					

* *Probability calculated on the basis of Fischer's exact test*

Clinical signs as individual predictors of positive EMG findings

When taken into consideration individually, three clinical trials have been shown to be discriminatory in terms of verification of radiculopathy: a positive test of Lazarevic, a paresis of a particular muscle group, and the absence or reduction of the patellar or Achilles reflex (Table 3). However, after the processing by logistic regression, the statistical predictive value is retained by a positive Lazarevic test (Table 4).

Although Table 5 indicates that the sum of specific clinical signs shows a statistically significant predictor property, the analysis of the surface under ROC curve shows that it is only in a zone of poor diagnostic significance.

Table 4. Clinical signs as individual predictors of positive EMG findings

Sign	b	SEb	P	OR (95% i.p.)	
Bellov sign	0.48	0.55	0.375	1.62	0.56-4.74
Schober sign	-0.90	0.51	0.076	0.41	0.15-1.10
Lazarević sign	1.44	0.48	0.003	4.20	1.64-10.80
Sensitivity drop	-0.29	0.51	0.572	0.75	0.28-2.03
Reflex absent	0.69	0.54	0.206	1.99	0.69-5.75
Weakness of myotoma	0.92	0.62	0.139	2.51	0.74-8.51

The overall model is statistically significant : χ2(6) = 21,27, P = 0,002

Table 5. Significance statistics for the sum of clinical trials

	b	SEb	P	OR (95% i.p.)		ROC površina (95% i.p.)	
Sum of clinical signs	0.45	0.18	0.014	1.57	1.10 - 2.26	64.8	(54.6 - 74.1)

Table 6. Classification table based on the number of clinical signs

	Electromyonurographic finding			
	Negative		Pozitive	
No. of clinical signs	n	%	n	%
0	0	0.0	0	0.0
1	4	66.7	2	33.3
2	8	53.3	7	46.7
3	12	38.7	19	61.3
4	7	26.9	19	73.1
5	5	22.7	17	77.3
6	0	0.0	0	0.0

Table 6 shows the classification based on the number of clinical signs, and Table 7 is the diagnostic classification value based on the number of clinical signs.

Table 7. Diagnostic classification value based on the number of clinical signs

No. of clinical signs	Sensitivity	95% i.p.	Specificity	95% i.p.
1 and more	100	94.3-100.0	0	0.0-9.8
2 and more	96.87	89.1-99.5	11.11	3.2-26.1
3 and more	85.94	75.0-93.3	33.33	18.6-51.0
4 and more	56.25	43.3-68.6	66.67	49.0-81.4
5	26.56	16.3-39.1	86.11	70.5-95.3

** Maximum value of the Iouden index, which, statistically speaking, represents an optimal limit value*

The positivity of four or more clinical tests is statistically the best limit value, with a specificity of 67% and a sensitivity of 56% in the diagnosis of LS radiculopathy (EN1).

Discussion

The values of the clinical findings are being increasingly neglected in relation to excessive and almost exclusive use of visualization methods of testing. However, an isolated clinical trial of patients with symptoms of lumbar radiculopathy does not often give satisfactory conclusions. Electrophysiological examination can be very useful in the diagnosis of lumbosacral radiculopathies by determining the degree and level of the lesion, but also by excluding the existence of peripheral nervous lesions due to other causes. The true diagnostic accuracy and the value of clinical trials of lumbar radiculopathies provokes numerous debates. The sensory deficit, the absence of deep tendon reflexes, and motor weakness may be present at a different degree of manifestation and in different diseases. The loss of tendon reflexes is often taken with the utmost certainty to confirm the actual radiculopathy: the patellar reflex for the roots L2 and L3, the variable reflex m. tibialis post. for the root of L5, and Achill's root-root reflex S1. It is generally accepted that these clinical tests record good specificity, but low sensitivity. In our research, the asymmetry of reflex, muscle paresis and Lazarević's sign show a predictive diagnostic value for lumbosacral radiculopathies, but in total with poor diagnostic significance precisely because of low sensitivity.

In any case, the values of the specificity and sensitivity of particular clinical data obtained in this study are slightly lower than previously published. The differences in studies originate primarily from differences in the population sample, and partly in the different designs of studies.[11]

In our study, the positive finding of the defined clinical trials was not an including factor for entering the study, and therefore potential verification burden was avoided.[12] It is also evident that our examination included a sample of general population without isolating specific population samples, thereby avoiding new restrictions. For example, both sexes are equally represented, while the majority of the previous trials included approximately twice as many men. In order to avoid asymptomatic patients and insignificant problems, only patients with severe pain in the lower part of the back that radiated to the legs and caused significant disability, were involved. These symptoms are generally accepted anamnestic parameters of acute lumbosacral radiculopathies.

According to the research, independent indicators of actual radiculopathy in the clinical finding are:

- Objective muscle weakness,
- Positive Lazarevic test,
- Absent reflex

Such findings are in line with existing clinical practice experience. It is surprising that there is no dermatomic sensitivity outbreak as a predictor of radiculopathy, although it was expected that the Schober test would be a predictor of radiculopathy, primarily due to the stretching of the meninge and roots, but also because of the reversal of lumbar lordosis, which has a mechanical protective effect on the present herniation of the disc. This sign did not prove to be predictive in this study. The position of the lumbar spine opens up the space of the last part of the intervetebral space and could aggravate and intensify the present herniation. However, most other causes of pain in the back of non-radicular etiology would limit this movement. For this reason, the anteflective test is insufficiently specific.[13] It appears that this test also indicates the irritation and tension of the root, and not just the compression.[14] The clinical sign of lifting the stretched leg, that is, Lazarević's sign, was the only one among the studied clinical trials proved predictive and through statistical method of logistic regression. This finding is expected because this sign proved to be highly sensitive (91%), but low in specificity (up to 45%).[15, 16]

Conclusion

The performed study indicates the statistical significance of the clinical tests of the raised leg, i.e. the Lazarevic test, the objective weakness of the muscle and the absent reflex, in the diagnosis of lumbosacral radiculopathy. A detailed clinical examination can lead to a quicker and easier diagnosis, as well as to significant savings in the healthcare system, avoiding often unnecessary additional diagnostic procedures.

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Procjena vrijednosti kliničkih testova na osnovu elektrofiziološki verifikovane lumboishijalgije

SAŽETAK

Uvod: Lumboishijalgija se definiše kao bol u distribuciji ishijadičnog nerva uzrokovana patološkom promjenom samog nerva, dok je lumbago lokalizovani spondilogeni bol koji nije praćen neurološkim deficitom i posljedica je mišićno koštane disfunkcije lumbosakralne regije. Dosadašnje studije koje su istraživale vrijednost kliničkih testova u dijagnostici lumboishijalgija nisu našle visoku senzitivnost i specifičnost ispitivanih testova.

Cilj rada: Cilj nam je bio definisati kliničke testove koji ukazuju na postojanje radikulopatije i utvrditi vrijednost cjelokupnog dijagnstičkog nalaza u odnosu na nalaz EMNG pregleda.

Metode: Istraživanje je provedeno na uzorku od 100 pacijenta, oba pola, starosti od 18-65 godina. Inkluzioni kriterijumi su bili jak bol u donjem dijelu leđa sa širenjem u jednu ili obe noge u trajanju od jednog do tri mjeseca i klinička slika koje jasno sugeriše postojanje radikularne lezije. Ekskluzioni kriterijumi su bili: simptomi caudae equinae, akutna febrilna stanja, postojanje tumora, frakture pršljenova, lezije centralnog motornog neurona, akutna psihotična stanja, nemogućnost elektromiografskog pregleda. Svakom EMNG pregledu je prethodio detaljan klinički pregled.

Rezultati: Pacijenti najčešće imaju ukupno dva (31%) i tri (26%) pozitivna klinička znaka lumboishijalgije. Statističkom analizom tri klinička testa su se pokazala diskriminativna u pogledu verifikacije radikulopatije: pozitivan test Lazarevića, pareza određene mišićne grupe, te odsustvo ili redukcija patelarnog ili Ahilovog refleksa. Nakon obrade logističkom regresijom, statistički prediktivnu vrijednost zadržava pozitivan test Lazarevića. Analiza površine pod ROC krivom pokazuje da pozitivnost četiri i više kliničkih testova predstavlja statistički gledano najbolju graničnu vrijednost, sa specifičnošću od 67% i senzitivnošću od 56%.

Zaključak: Provedena studija ukazuje na statističku značajnost učestalosti pozitivnih kliničkih testova: Lazarević testa, objektivne slabosti mišića i ispada refleksa, kod osoba sa elektrofiziološki verifikovanom lumboishialgijom.

Ključne riječi: lumboishijalgija, klinički testovi, EMNG

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Effects of Anxiety and Depressive Manifestations of Personality on Functional Recovery of Patients with Cervical Pain Syndrome

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ABSTRACT

Introduction: Cervical syndrome is a set of symptoms that are manifested by pain in the neck segment and shoulder blade region, with the feeling of tightness and tension, and limited movement of the neck segment of the spine. Because of the long-term duration of symptoms, we often find psychopathological manifestations in the form of anxiety and depression in these patients.

Objective: The goal was to detect the presence of anxiety and depressive manifestations of personality in patients with cervical syndrome at the beginning of rehabilitation treatment, to determine to what extent the presence of anxiety and depressive symptomatology affects the functional recovery of patients after a physical rehabilitation treatment.

Patients and Methods: The study was conducted as a prospective study involving 100 patients. Criteria for inclusion were the diagnosis of cervical syndrome and the age of patients between 20 and 60 years of age. Exclusion criteria were diagnosis of cervical radiculopathy, vertebrobasilar syndrome, diagnosis of anxiety and depressionconfirmed by psychiatrist, as well as use of psychotropic substances. On admission, each patient filled in Beck's questionaire for anxiety and depression (BAI and BDI)and accordingly patients were divided into 3 groups.

Results: Out of total of 100 patients, 74% were female and 26% were male. In 77% of patients psychopathological manifestations of personality were found. A statistically significant association of gender and group placement was found (p=0,003). The women had a far greater percentage of anxiety and anxiety-depressive manifestations of the personality than men. In terms of BAI and BDI, there was a statistically significant difference between genders. All of the parameters (VAS, Schober, CSS) monitored during rehabilitation treatment were improved at the end of treatment (p=0,0001). There was a positive correlation of BAI and BDI with CSS on admission and at discharge (p=0,05) in a group of anxiety-depressed patients.

Conclusion: The presence of anxiety and depressive manifestations of personality did not have a negative impact on the functional recovery of patients. Physical therapy has led to reduction of pain, increased mobility and better functional status of cervical spine for patients with cervical spine syndrome.

Key words: cervical syndrome, functional recovery, depression, anxiety

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Introduction

Cervical syndrome is a set of symptoms that are manifested by pain in the neck segment and shoulder blade region, with the feeling of tightness and tension, and limited movement of the neck segment of the spine. In some cases, pain can spread towards the back of the head, in which case we are talking about cervicocranial syndrome (Syndroma cervicocraniale), or towards the shoulder and arm when we talk about cervibrachiale syndrome (Syndroma cervicobrachiale).[1,2]. The causes of the onset of this painful state are numerous, but the most common cause is the degenerative diseases of the vertebra and intervertebral discs.[1,2,3] In addition, cervical syndrome can also occure due to injuries in the cervical spine region, inflammatory rheumatism, infections as well as in malignant diseases.

Risks for developing this disorder are related with working in poor microclimatic conditions and in the non-physiological position of the body. The majority of patients fall into the working age population, aged between 40 and 55 years.[4,5,6]

Resulting changes in affected cervical spine and surrounding soft tissues cause pain wich in turn results in reduction of mobility, weaknes and increased muscle tension , and consequently a poorer quality of life.[7] In order to alleviate the symptoms of these patients, several types of therapies are applied which can reduce the symptoms, reduce pain and improve the function of the cervical spine. Physical therapy is, in addition to medication and education of patients, the basis of conservative treatment for this painful condition.[8,9]

Because of the long-term duration of symptoms, we often find psychopathological manifestations in the form of anxiety and depression in these patients.[10,11,13] These symptoms should be noted on the first encounter with patient because they can slow down functional recovery. Team approach to this issue can provide comprehensive treatment aimed to relieve symptoms as well as a timely professional and social reintegration.

The goal of his research was to detect the presence of anxiety and depressive manifestations of personality in patients with cervical syndrome at the beginning of rehabilitation treatment, to determine to what extent the presence of anxiety and depressive symptomatology affects the functional recovery of patients after a physical rehabilitation treatment.

Objective

The goal was to detect the presence of anxiety and depressive manifestations of personality in patients with cervical syndrome at the beginning of rehabilitation treatment, to determine to what extent the presence of anxiety and depressive symptomatology affects the functional recovery of patients after a physical rehabilitation treatment.

Patients and Methods

Research was conducted as a prospective study wich included 100 patients of both gender. Criteria for inclusion were the diagnosis of cervical syndrome (pain in the neck and shoulder blade region lasting longer than 6 months, feelling of tension, limited mobility of cervical spine) and the age of patients between 20 and 60 years of age. Exclusion criteria were diagnosis of cervical radiculopathy, vertebrobasilar syndrome, diagnosis of anxiety and/or depression confirmed by psychiatrist, as well as use of psychotropic substances. On admission, each patient filled in Beck's questionaire for anxiety and depression (BAI and BDI) and accordingly patients were divided into 3 groups. First group – no manifestations, included 32 patients, second group- anxiety personality manifestations included 41 patients, and third group- anxiety-depressive personality manifestations included 21 patients. Each patient was assessed on admission and at discharge using Cervical Spine Score (CSS) for cervical spine function, Visual Analogue Scale (VAS) for pain intensity and Schober's index of sagittal mobility for cervical spine. All patients were treated as stationary patients at Depratment V of Rehabilitation centre „dr Miroslav Zotović", Banja Luka, in average of 19 days (mean 19,07 st.dev 1,8 days). Their treatment included therapeutic exercise treatment and application of other physical therapy modalities. Patients who had anxiety and depressive manifestations of personality were included in relaxation groups under the supervision of a psychologist. This research was approved by the Ethics Committee. Each patient signed the Informed consent to participate. The obtained data were statisticaly analyzed using the following statistical tests, parametric(independent Student T test, ANOVA, Tukey test) and non-parametric(Mann Witnney, Kruskal Wallis test).

Results

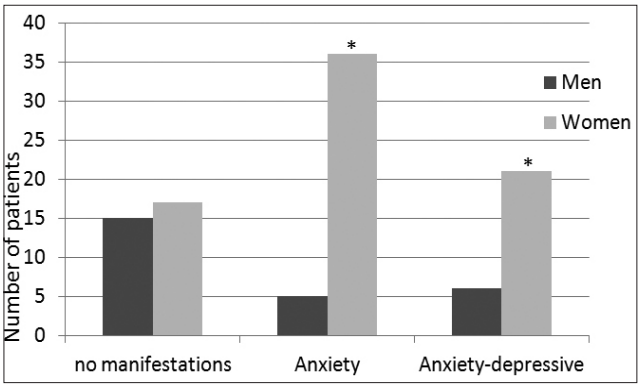
In this study, out of a total of 100 patients, 74% were women and 26% were men. There were no significant differences in age between men and women (Table 1).

Table 1. Patient distribution by age

Gender	N	Mean (age)	St. dev.
M	24	53.31	7.55
F	76	55.50	7.72
Total	100	54.93	7.30

In 77% of the patients, psychopathological manifestations of the personality (anxiety and anxiety-depressive) were found. The statistically significant association of gender and belonging to the group (x2 = 11.5; p = 0.003, Figure 1) was found. The women were in a far greater percentage for anxiety and anxiety -depressive disorder.

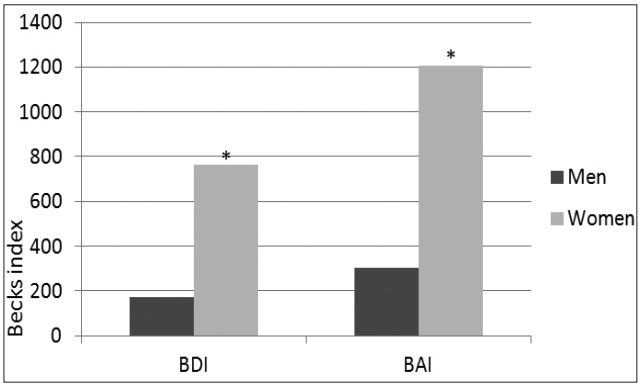
Figure 1. Gender representation in groups of patients without and with anxiety and anxiety / depressive manifestations of the personality.



** p = 0.003 versus men within the same manifestation of personality.*

There was a statistically significant difference between men and women regarding the BDI and BAI (women have higher scores, Figure 2).

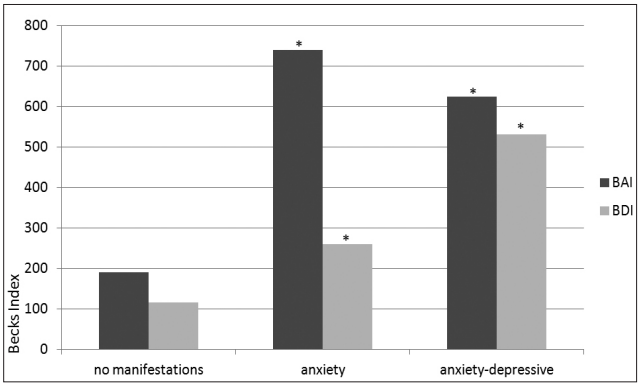
Figure 2. Values of Beck's Depression Index (BDI) and Beck's Anxiety Index (BAI) versus gender



** p = 0.003, women versus men within the same index*

Statistically significant difference between groups was found regarding BAI and BDI (Figure 3).

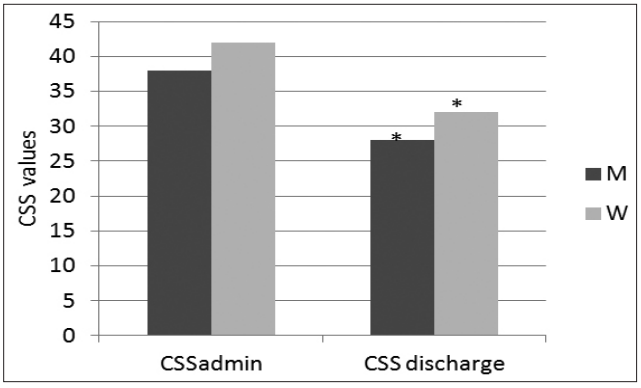
Figure 3. Values of the Beck Anxiety Index (BAI) and Depression (BDI) in the patient groups



** p <0.05 versus the values in the group without manifestations*

In terms of CSS on admission and at discharge, there is no gender difference, but it is clear that the values of these scores are reduced after treatment because they are significantly lower at disharge (Figure 3a).

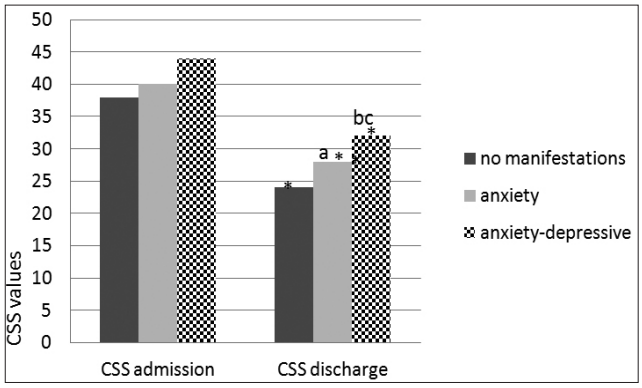
Figure 3a. Values of Cervical Spine Score (CSS) before (CSSadmin) and after physical therapy (CSSdischarge) in patients of both gender



** P <0.05 relative to the CSSadmin value (CSSadmin)*

Statistically significant difference between groups was found in CSS on admission and CSS at discharge (Figure 4). CSS values before and after physical therapy were such that the spine function in all three groups of patients was improved at discharge (Figure 4). While the CSS values of the three groups of patients did not differ on admission, CSS at discharge were significantly worse in the group with anxiety, and especially with anxiety-depressive manifestations of the personality (Figure 4).

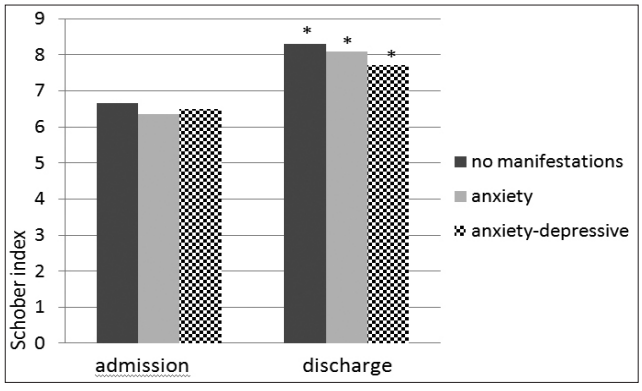
Figure 4. Values of Cervical Spine Score (CSS) before and after physical therapy in groups of patients.



** p = 0.05 relative to CSS on admission. a- p <0.05 CSS in patients with anxiety disorder compared to the group without psychopathological manifestation of personality, b - p <0.05 CSSdischarge in patients with anxiety-depressive manifestation of personality in relation to a group without a psychopathological manifestation of personality, c - CSSdischarge in patients with anxiety-depressive manifestation of personality in relation to a group of patients with anxiety manifestation of personality.*

Regarding the mobility of the cervical spine, a significant increase in mobility was observed in all groups at discharge compaired to admission, mostly in the group without disorders and in the group of anxiety manifestations, and the least in the group of anxiety-depressive manifestations (Figure 5).

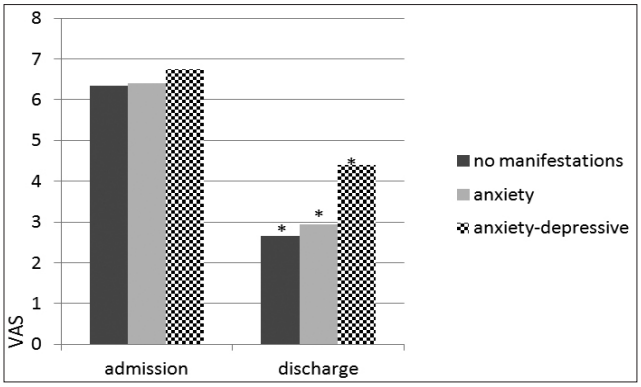
Figure 5. Mobility of the cervical spine measured by the Schober index on admission and at discharge



** P = 0.0001 compared to the value of Schober's index on admission*

In terms of the intensity of the pain examined by the visual analogue scale of the pain (VAS),we found a significant decrease in the value, reduction of pain for all three groupsat discharge compaired to admission (Figure 6).

Figure 6. Score on visual analogue scale (VAS) for admission and discharge



** p = 0.0001 in relation to the value of VAS on admission*

Through comparison of the BAI values with three functional tests prior to the start of physical therapy we found a statistically significant correlation only between BAI and CSS (Table 2).

Table 2. Correlations of the Beck Anxiety Index (BAI) and the value of the functional tests on admission

Parameter	BAI	Schober-adm	CSSadm	VASadm
BAI		NS	0.001	NS
Schober-pr	NS		NS	NS
CSSpr	0.001	NS		NS
VASpr	NS	NS	NS	

Through comparison of the BDI values with three functional tests prior to the start of physical therapy we found a statistically significant correlation only between BDI and CSS (Table 3).

Table 3. Correlations of the Beck Depression Index (BDI) and the value of the functional tests on admission

Parameter	BDI	Schober-adm	CSSadm	VASadm
BDI		NS	0.001	NS
Schober-pr	NS		NS	NS
CSSpr	0.001	NS		NS
VASpr	NS	NS	NS	

When the differences between the values of these parameters on admission and discharge are calculated and when they are expressed in percentage of the value on admission we got results that are shown in Table 4.

Table 4. Percentual changes in parameters (ΔSchober, ΔCSS and ΔVAS) in patients without disorders and with anxiety and anxiety-depressive disorder

Parameter	Group	N	Mean	Std. Error	Signifi-cance
ΔSchober	1	32	29.49	4.59308	n/a
	2	41	29.35	4.94016	NS
	3	27	20.24	2.73579	NS
ΔCSS	1	32	69.98	2.17091	n/a
	2	41	76.01	1.98804	NS
	3	27	82.9	1.78019	p<0,05
ΔVAS	1	32	44.77	3.49557	n/a
	2	41	49.17	2.70067	NS
	3	27	54.32	4.46114	NS

ΔSchober, ΔCSS and ΔVAS - differences in the values of the parameters of the drive and release, expressed in percentages of the receive value. P <0.05 - significance in relation to a group of patients without psychopathology. 1 - Group of patients without psychopathology, 2 - Group of patients with anxiety manifestation of personality, 3 - Group of patients with anxiety-depressive manifestation of personality.

Among these monitored parameters, only the value of ΔCSS in the group of patients with anxiety-depressive personality disposition reached statistical significance in relation to the group without psychopathological manifestations of the personality, although the value of the same parameter in the group with anxiety manifestation the personality was close to the statistical significance threshold (p <0.052). Although the values of other parameters in patients with depressive, and especially with anxiety-depressive personality disposition tend to be worse than in patients without psychopathological symptomatology, these differences did not reach statistical significance.

Tables 5, 6 and 7 show Pearson's correlations between the depression and anxiety parameters (BDI, BAI) and values of fuctional tests expressed as a percentage change (improvement) at discharge compared to those at admission (ΔSchober, ΔCSS, ΔVAS), and specifically for each group of patients (without symptoms, with anxiety and anxiety-depressive manifestation of personality).

In patients without anxiety and depressive manifestations of the personality, a correlation between the results of BDI and BAI was found, as well as between the values of ΔSchober and ΔCSS, and ΔVAS (Table 5).

Table 5. Correlations between depression and anxiety tests (BDI, BAI) and improvement of functional parameters on discharge, expressed as a percentage of their admission values (ΔSchober, ΔCSS and ΔVAS) in patients without anxiety and anxiety-depressive manifestations

Parameter	BDI	BAI	Δ Schober	ΔCSS	ΔVAS
BDI		<0.01	NS	NS	NS
BAI	<0.01		NS	NS	NS
ΔSchober	NS	NS		NS	<0.01
ΔCSS	NS	NS	NS		<0.05
ΔVAS	NS	NS	<0.01	<0.05	

NS – not significant

In patients with anxiety symptoms, the correlation was found only between BDI and BAI values (Table 6).

Table 6. Correlations between depression and anxiety tests (BDI, BAI) and improvement of functional parameters on discharge, expressed as a percentage of their admission values ΔSchober, ΔCSS and ΔVAS in patients with anxiety manifestation of personality

Parameter	BDI	BAI	Δ Schober	ΔCSS	ΔVAS
BDI		<0.01	NS	NS	NS
BAI	<0.01		NS	NS	NS
ΔSchober	NS	NS		NS	NS
ΔCSS	NS	NS	NS		NS
ΔVAS	NS	NS	NS	NS	

NS – not significant

In patients with anxiety-depressive symptoms, correlations between BDI i BAI, and also between ΔSchober, ΔCSS and ΔVAS (Table 7) were found.

Table 7. Correlations between depression and anxiety tests (BDI, BAI) and improvement of functional parameters on discharge, expressed as a percentage of their admission values ΔSchober, ΔCSS and ΔVAS) in patients with anxiety-depressive symptoms

Parameter	BDI	BAI	Δ Schober	ΔCSS	ΔVAS
BDI		<0.01	NS	NS	NS
BAI	<0.01		NS	NS	NS
ΔSchober	NS	NS		<0.01	<0.05
ΔCSS	NS	NS	<0.01		<0.01
ΔVAS	NS	NS	<0.05	<0.01	

NS – not significant

Discussion

The results of this study showed that 77% of the patients involved in the study had some form of psychopathological manifestation of the personality. The presence and intensity of these disorders did not have a negative effect on the functional recovery of patients after a physical rehabilitation treatment. We found a statistical improvement in terms of increased mobility of cervical spine and reduced pain , in all three groups at discharge comparing to admission ($p < 0.0001$).

Physical therapy has led to a statistically significant improvement in the cervical spine function (CSS), the smallest improvement was in group 3 (difference between groups 1 and 3, 2 and 3 at discharge $p < 0.05$). The presence of anxiety and depressive manifestations of the personality did not significantly affect the outcome of the physical rehabilitation treatment in terms of reduced pain and increased mobility of the spine in all three groups of patients, but had an effect in terms of lesser functional recovery in the group of anxiety depressive patients. In order to reduce the discomfort of these patients, different types of therapy are used, primarily therapeutic exercises that can relieve symptoms, as in reduce pain and improve the function of the cervical spine.[20,21] Engaging patients in relaxation groups under the supervision of psychologists can mitigate anxiety and depressive symptomatology and contribute to faster recovery of patients.

The association of anxiety and depression with chronic neck pain was demonstrated by a group of experts through a national cross-section study conducted in 19 countries (52,095 participants). It was concluded that the earlier onset of mental disorders was a strong predictor of pain in the neck compared to the later onset.[10]

The correlation of various mental disorders with 10 different pain syndromes has been demonstrated by a group of experts with a cross section study involving 17 countries (47,609 participants). Accent was placed on the primary prevention of chronic pain conditions as part of the treatment of all mental disorders at the primary and secondary levels.[11]

A group of Turkish authors has shown that anxiety disorders and mood swings are often found in patients with lumbar and cervical herniation of the intervertebral disc or without herniation. Anxiety disorders and mood swings were associated with pain, but they also found an association with neurological deficits.[12]

On the other hand, a group of Dutch authors followed 1121 patients with chronic pain syndrome and concluded that pain, rather than chronic illness, lead to the occurrence of anxiety disorders and worsening of depression.[13,14]

Wasan et al.[15] have shown that psychiatric disorders and imparing of the quality of life are more common in men with chronic back pain on the left side then in women. This was explained by the fact that in men the right hemisphere of the brain is predominantly involved in processing the pain.

There are several limitations of our research: uneven representation of female and male sex (74/26) as well as the fact that patients are recruited from one health institution.

In the available literature, no data on the influence of psychopathological manifestations on the outcome of physiorehabilitation treatment were found, which contributes to the originality of the results of our study.

This study has shown that physical therapy has a positive effect on pain reduction, increase of the range of motion in the cervical spine, and the improvement of the functional status of the cervical spine in patients with cervical pain syndrome. The presence of anxiety and depressive manifestations of the personality has slowed down the functional recovery for a group of patients with anxiety and depressive manifestations inasmuch as the intensity of these disorders was higher, but did not have an effect on the reduction of pain and mobility of the cervical spine. Therefore, it is important to emphasize the importance of early assessment of the psychological status of patients with cervical pain syndrome in order to achieve faster and better results through comprehensive physical treatment and relaxation techniques.

Conclusion

The presence of anxiety and depressive manifestations of personality did not have a negative impact on the functional recovery of patients. Physical therapy has led to reduction of pain, increased mobility and better functional status of cervical spine for patients with cervical spine syndrome.

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Uticaj anksioznih i depresivnih ispoljavanja ličnosti na funkcionalni oporavak pacijenata sa cervikalnim bolnim sindromom

SAŽETAK

Uvod: Cervikalni sindrom predstavlja skup simptoma koji se manifestuju bolom u vratnom segmentu i rameno-lopatičnoj regiji ali i osjećajem zatezanja i napetosti, te ograničenih pokreta vratnog segmenta kičme. Zbog dugotrajnosti simptoma često kod ovih pacijenata možemo naći psihopatološka ispoljavanja u vidu anksioznosti i depresije.

Cilj rada: Cilj je bio detektovati na početku rehabilitacionog tretmana prisustvo anksioznih i depresivnih ispoljavanja ličnosti kod pacijenata sa cervikalnim sindromom, ispitati koliko prisustvo anksiozne i depresivne simptomatologije utiče na funkcionalni oporavak pacijenata nakon provedenog fizikorehabilitacionog tretmana.

Pacijenti i metode: Istraživanje je provedeno kao prospektivna studija u koju je uključeno 100 pacijenata. Kriterijumi za uključenje su bili dijagnoza cervikalnog sindroma istarost pacijenata od 20-60 godina. Kriterijumi za neuključenje su bili dijagnoza cervikalne radikulopatije, vertebrobazilarnog sindroma, od strane psihijatra potvrđena anksioznost i depresija kao i uzimanje psihotropnih supstanci. Na prijemu je svaki pacijent popunjavao Beckov upitnik za anksioznost i depresiju (BAI i BDI) i prema tome su pacijenti podijeljeni u 3 grupe.

Rezultati: Od ukupno 100 ispitanika 74% su bile žene i 26% muškarci.Kod 77% ispitanika su nađena psihopatološka ispoljavanja ličnosti.Utvrđena je statistički značajna povezanost pola i pripadnosti nekoj od grupa (p=0,003).Žene su u daleko većem procentu imale anksiozna i anksiozno-depresivna ispoljavanja ličnosti nego muškarci. Nađena je statistički značajna razlika između polova kada je riječ o BDI I BAI. Svi praćeni parametri (VAS, Schober, CSS) nakon provedenog fizikorehabilitacionog tretmana su u svim grupama poboljšani na otpustu (p=0,0001). Nađena je pozitivna korelacija BAI i BDI sa CSS-om na prijemu i otpustu (p=0,05) u grupi anksiozno depresivnih pacijenata.

Zaključak: Prisustvo anksioznih i depresivnih ispoljavanja ličnosti nije imalo negativan uticaj na funkcionalni oporavak pacijenata. Fizikalna terapija kod pacijenata sa cervikalnim sindromom je dovela do smanjenja bola, povećanja pokretljivosti i boljeg funkcionalnog statusa vratne kičme.

Ključne riječi: cervikalni sindrom, funkcionalni oporavak, depresija, anksioznost

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Analysis of Survival at Metastatic Melanoma Patients Treated with Vemurafenib - a Three Year Single Institution Study

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ABSTRACT

Introduction: The introduction of BRAF inhibitor vemurafenib significantly improved overall survival (OS) in metastatic melanoma patients.

Aim of the Study: The purpose of this study was to determine OS and progression free survival (PFS) in patients with advanced metastatic melanoma treated with vemurafenib in the Oncology Clinic, University Clinical Centre of the Republic of Srpska (UKC RS). The secondary goal is to determine the effect of elevated serum lactate dehydrogenase (LDH) on OS.

Patients and Methods: We analysed patients that received vemurafenib in the April 2015. until March 2018. They had pathohistologically confirmed B-RAF positive metastatic melanoma. LDH values were measured at the start of the treatment.

Results: A total of 16 patients were analyzed, with an average age of 53 years (37-78). A large number of patients at the start had multiple sites of metastases. Calculated OS in patients who received vemurafenib is 11.8 months (p=0,23), with standard deviation (SD) 9.18. The calculated PFS is 9.5, SD 7,57. OS in patients with normal LDH is 14.4 months, SD 10.73, and with elevated LDH is 8.4 months, SD 4.9 (p=0.079).

Conclusion: Use of vemurafenib resulted in an improvement in PFS, with improved OS in patients with advanced BRAF-mutated melanoma. In patients with elevated LDH OS was reduced. This shows that LDH is a good prognostic marker and that we should do it routinely for all patients with melanoma. This study has indicated the need for new diagnostic and therapeutic options for melanoma in Republic of Srpska.

Key words: metastatic melanoma; BRAF mutation; vemurafenib

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Introduction

At the start of 21st century, melanoma remains a potentially fatal malignancy. At a time when the incidence of many tumor types is decreasing, melanoma incidence continues to increase.[1] According to data collected during the period 1998-2002, Mackie and colleagues showed that the highest recorded incidence of melanoma worldwide is in Queensland (Australia), where there is an incidence equal to $55.8/10^5$/annum for males and $41.1/10^5$/annum for females. Incidence rates vary for Europe and are highest in Switzerland and the Scandinavian countries, but recent data show a rise in incidence in many East European countries.[1] Although most patients have localized disease at the time of the diagnosis and are treated by surgical excision of the primary tumor, many patients develop metastases.[2] About five year ago treatment of patients with metastatic melanoma was limited to use of cytostatic drugs, their combinations and imunotherapy with cytokines.

In metastatic melanoma (American Joint Committee on Cancer (AJCC) stage IV), the prognosis was poor, and the median OS time was 6–12 months only.[3,4] Randomized trials have failed to demonstrate a benefit of a particular regimen[4], until 2011 when first results of phase 1 and 2 clinical trials of the BRAF kinase inhibitor vemurafenib (PLX4032) have shown response rates of more than 50% in patients with metastatic melanoma with the BRAF V600E mutation.[5]

Approximately 40 to 60% of cutaneous melanomas carry mutations in BRAF that lead to constitutive activation of downstream signaling through the MAPK pathway. Approximately 90% of these mutations result in the substitution of glutamic acid for valine at codon (BRAF V600E), although other activating mutations are known (e.g., BRAF V600K and BRAF V600R).[6,7]

Chemotherapy has limited success in metastatic melanoma, with responses noted in 6.3–12.1% of patients, and a median OS of 5.6–9.7 months in phase 3 trials of dacarbazine.[8-11] Combinations of cytostatic drugs and cytokines have not improved survival.[12,13] Highdose interleukin 2 can induce complete remission in some patients, which was the basis of its approval,[14] but no predictive biomarkers for the patient's response exist. In 2011, with the approval of the CTLA-4 antibody ipilimumab for all patients with advanced disease and of the BRAF inhibitor vemurafenib for BRAF-mutated disease, treatment for advanced disease finally improved.[5,15] In final overview of BRIM-3 study at the time of database lock (14 August 2015), median OS, censored at crossover, was significantly longer for vemurafenib than for dacarbazine, 13.6 for vemurafenib [95% confidence interval (CI) 12.0-15.4] and for dacarbazine 9.7 months [95% (CI) 7.9-12.8].[16]

Serum lactate dehydrogenase (LDH) has been shown to be a prognostic factor in patients with metastatic melanoma. Increased LDH values indicate tumor aggression and potential for metastasis and early relapses. However, LDH is a marker with high specificity, but with low sensitivity.[17,18]

Aim of the Study

The purpose of this study is to determine OS and PFS in patients with advanced metastatic melanoma treated with vemurafenib in Oncology Clinic, University Clinical Centre of the Republic of Srpska (UKC RS) and compare it with results of BRIM-3 clinical trial. The secondary goal is to determine the effect of elevated serum LDH on OS in the same patient group.

Patients and Methods

We initiated a non-randomized opservational retrospective/prospective study attempting to investigate whether patients that received targeted therapy with vemurafenib have similar OS, compared to BRIM-3 clinical trial. Study was performed in period from April 2015 to March 2018 in Oncology Clinic, UKC RS. The patients had pathohistologicaly confirmed B-RAF positive metastatic melanoma. A tissue samples were analysed in Department of pathology UKC RS to confirm the V600 BRAF mutation. A total of 19 patients received therapy (n=19), but 16 patients (n=16) were included in analysis, because 3 patients failed to take therapy more than 2 months. Patients were aged >18 years, had unresectable stage IIIC or stage IV (IIIC, M1a, M1b or M1c) melanoma with a BRAF V600 mutation and life expectancy of at least 3 months, Eastern Cooperative Oncology Group performance status (ECOG PS) 0-2 and adequate haematological, hepatic and renal function.

Every patient was presented and approved by a multidisciplinary tumour board. The primary end points were OS, defined as the time from the moment of follow up to death from any cause, and PFS, defined as the time from the start of follow up to documented disease progression or death. Patient received vemurafenib in dose of 960 mg orally twice daily in accordance with the guidelines. The co-primary objective was to determine OS in patients with elevated LDH (>200) and OS in patients with normal levels of LDH (≤200). LDH levels were measured before starting therapy with vemurafenib. Collected data were analyzed by descriptive statistical methods. We have also performed single sample Student`s t-test (one tail hypothesis test) to find out the test statistics. The Caplan-Meier curve was used

to show overall survival and survival in patients with different levels of LDH. The differences between the curves were evaluated using a log-rank test. For all the tests, we used the statistical program SPSS, version 23 (IBM SPSS Statistics for Windows, version 23.0, IBM Corp., Armonk, N.Y., USA).

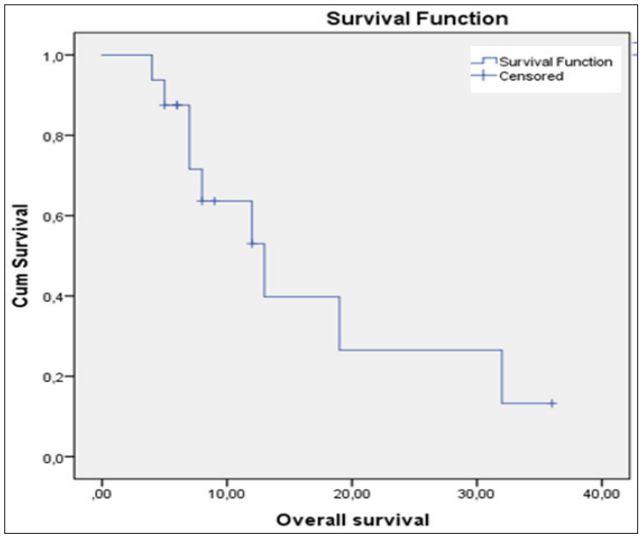
Results

A total of 16 patients were analyzed, ten males and six females, with an average age of 54,5 (37-78). Stage IV disease had a total of 12 patients (75%) and four patients had IIIC disease stage (25%). 10 patients had ECOG status 0 (62.5%), three patients had ECOG 1 (18,75%) and three patients had ECOG 2 (18.75%). The most affected organs (without lymph nodes) including also disease progression are shown in table 1.

Table 1. Most affected organs with metastases (overall monitoring)

Affected organs	(%)	Patients
Lung	37.5	6
Liver	37.5	6
Skin	37.5	6
Brain	31.25	5
Bones	18.75	3
Spleen	12.5	2

Picture 1. Caplan Meier curve which shows OS

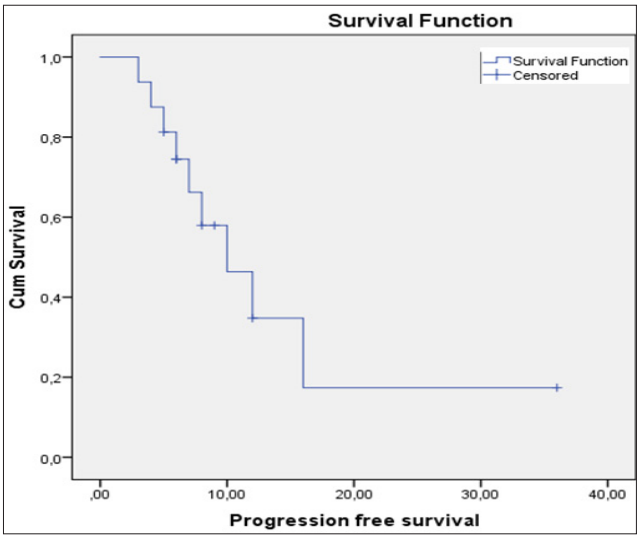


A large number of patients had at the start a multiple sites of metastases. It is important to note that 80% patients had metastases in the lymph nodes. The most common reason to switch off the therapy is because of progression of already existing metastases, or verified new mets in the brain. Most of the patients didn't have any post progression treatment. In most cases it was best supportive care, or some of them died immediately after progression (six patients). Two patients had salvage chemotherapy, without a major success, and in two patients a palliative brain irradiation was performed. Six patients are still alive with ongoing treatment.

Calculated median OS time in patients receiving vemurafenib from the moment of follow up until the end of March 2018 is 11,8 months (SD = 9,18, n=16) (picture 1).

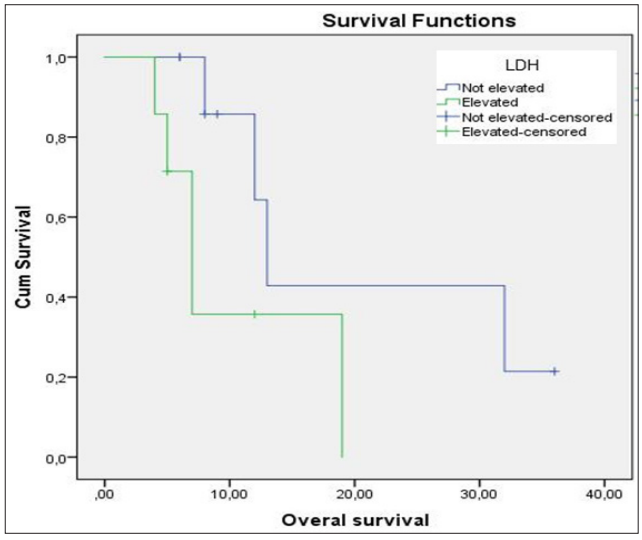
According to one-tailed single sample Student`s t-test, p=0.23 for level of significance α=0.05 when compared with vemurafenib group in BRIM-3 trial (OS=13,6 months) and p=0.183 when compared with dacarbazine group (OS=9.7 months). Calculated median PFS time in the same patient group was 9.5 months (SD = 7,57, n =16) (Picture 2).

Picture 2. Caplan Meier curve which shows PFS



By analysing LDH levels at the moment of starting vemurafenib therapy 7 patients had LDH values >200 U/L, and 9 patients were with normal LDH levels (≤200 U/L). The median overall survival was considerably longer in patients with normal LDH - 14,4 months, [95% (CI) 11-15], with SD of 10.73 n=9, than in patients with elevated LDH - 8.4 months, [95% (CI) 4.8-9.2], with SD of 4.9 n=7 (Picture 3). Statistical significance according to log rank test is 0.079.

Picture 3. **Caplan Meier curve which shows overall survival in patients with elevated levels of LDH (n = 7) and normal LDH (n = 9).**



Discussion

When taking into account results of phase 3 trials of dacarbazine that showed median OS of 5.6–9.7 months,[8-11] our results showed us increased OS in patients with metastatic melanoma treated with targeted therapy in comparasion with cythostatic treatment with dacarbazine. Also, reconsider weaknesses of the study (small patients sample and large standard deviation). Other cytostatics (Paclitaxel, Cisplatin, Temozolomid) showed even worse results than dacarbazine. We had similar results in OS in comparison with vemurafenib group in BRIM-3 study. Final results of BRIM-3 trial showed us that single-agent vemurafenib improve the rates of response and of both PFS and OS, as compared with dacarbazine, in patients with metastatic melanoma with the BRAF V600E mutation. OS censored at crossover was significantly longer for vemurafenib than for dacarbazine, 13.6 for vemurafenib [95% (CI) 12.0-15.4] and for dacarbazine 9.7 months [95% (CI) 7.9-12.8]. These findings provide a solid basis for the development of future therapies and their combinations.[16,19]

It is expected that with the ongoing development within combined MAP kinase inhibition (BRAF-MEK inhibition) and blockers of immune checkpoint molecules (PD-1 plus CTLA-4 inhibition), for example novel combination partners, new dosing regimens and intermittent schedules, there will be further prolongation of survival times in the near future.[20]

In randomized study, a combination of vemurafenib and cobimetinib (combination group) or vemurafenib and placebo (control group), the combination of vemurafenib and cobimetinib, as compared with vemurafenib alone, resulted in an improvement in PFS and objective responses, with early evidence of improved OS and a somewhat increased toxicity profile, among patients with advanced BRAF-mutated melanoma.[19,20] Similar results were found, in study with dabrafenib and trametinib compared to dabrafenib and placebo. Median OS was 25,1 months (95% CI 19,2-not reached) in the dabrafenib and trametinib group versus 18,7 months (15,2-23,7) in the dabrafenib only group.[21]

There is a superiority of combined BRAF plus MEK inhibition within the first 6 months after treatment onset,[22] however later, there is a change to a clear superiority of PD-1 blockers alone or in combination with CTLA-4 blockers.[23] In an analysis of available survival data from mayor clinical trials for the new treatment strategies in an updated exploratory analysis with follow-up times of 24 months or longer in the first-line setting, showed us new insights into the effect of different treatment strategies on long-term survival. The proportions of patients alive at 24 months were 53.5% with BRAF plus MEK inhibitor treatment versus 62.9% with PD-1 plus CTLA-4 blockade, and 59.3% with PD-1 inhibition alone, demonstrating a superiority of immune checkpoint blockade now at 24 months after treatment start.[23]

In patients with elevated LDH, overall survival is reduced. This shows that LDH is a good prognostic marker and that we should do it routinely for all patients with melanoma. According to this, the future researches would focus on determining correlations of LDH with survival, but on a much larger patients group and at different stages of the disease. As well, we can focus on the impact of other predictive biological markers, like S100B as serological marker for melanoma.

In conclusion, our study, despite all the weaknesses, compared to the results of BRIM-3 trial, showed similar results in overall survival and progression free survival. Even though, a large standard deviation and our sample of sixteen patients is not sufficiently large to provide a statistical proof of the significance. Compared to the results of cytostatic chemotherapy protocols, the use of targeted therapy with vemurafenib in patients with advanced BRAF-mutated melanoma, showed an improvement of response rates, progression free survival and overall survival. In patients with elevated LDH, overall survival is reduced.

This study has indicated the need for new therapeutic options for metastatic melanoma in the Republic of Srpska, better prevention and diagnostic. Access to

new treatment options and greater participation in international clinical studies, introducing new diagnostic methods in the form of blood biomarkers and creating local guidelines, can lead to an increase in therapeutic opportunities and prolongation of life in patients with metastatic melanoma.

Conclusion

Use of vemurafenib resulted in an improvement in PFS, with improved OS in patients with advanced BRAF-mutated melanoma. In patients with elevated LDH OS was reduced. This shows that LDH is a good prognostic marker and that we should do it routinely for all patients with melanoma. This study has indicated the need for new diagnostic and therapeutic options for melanoma in Republic of Srpska.

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metastatic melanoma: the impact of novel therapies-update 2017. Eur J Cancer 2017;83:247–57.

Uticaj vemurafeniba na preživljavanje kod pacijenata sa metastatskim melanomom, trogodišnja analiza

SAŽETAK

Uvod: Uvođenje BRAF inhibitora vemurafeniba značajno je poboljšalo ukupno preživljenje (overall survival-OS) kod pacijenata sa metastatskim melanomom.

Cilj rada: Svrha ove studije je utvrditi OS i preživljavanje bez progresije bolesti (progression free survival-PFS) kod bolesnika sa metastatskim melanomom liječenim vemurafenibom u Klinici za onkologiju Univerzitetskog kliničkog centra Republike Srpske (UKC RS). Sekundarni cilj je odrediti uticaj povišene serumske laktat dehidrogenaze (LDH) na OS.

Ispitanici i metode: Analizirani su bolesnici koji su primili ciljanu terapiju sa vemurafenibom u periodu od 4/2015. do 3/2018. i kod svih je potvrđena BRAF mutacija. Takođe, određivana je vrijednost LDH prije početka tretmana.

Rezultati: Ukupno 16 pacijenta je analizirano, sa prosječnom starosti 53 godine (37-78). Većina pacijenata je u startu imala metastaze u više različitih organa. Srednje OS od momenta praćenja zaključno sa martom 2018. je 11,8 mjeseci (p=0.23), standardna devijacija (SD) je 9,18. Izračunato srednje PFS kod iste grupe pacijenata je 9,5, SD je 7,57. OS je znatno duži kod pacijenata sa normalnim vrijednostima LDH (14.4 mjeseci), SD 10.73, nego kod pacijenata sa povišenim vrijednostima LDH (8,4 mjeseca) SD 4,9 (p=0.079).

Zaključak: U poređenju sa rezultatima primjene citostatskih hemioterapijskih protokola, upotreba vemurafeniba rezultirala je poboljšanjem PFS-a i OS-a kod pacijenata sa uznapredovalim BRAF-mutiranim melanomom. Kod bolesnika sa povišenim LDH smanjen je OS. Ovo pokazuje da je LDH dobar prognostički marker i da ga treba raditi rutinski kod svih pacijenata oboljelih od melanoma. Ova studija je ukazala na potrebu novih dijagnostičkih i terapijskih opcija za metastatski melanom u Republici Srpskoj.

Ključne riječi: metastatski melanom; BRAF mutacija; vemurafenib

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Open Surgical Biopsy in Diagnosis of Mammographically Detected Suspicious Microcalcifications

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ABSTRACT

Background: One of the earliest signs of breast cancer may be the presence of mammographically detected suspicious microcalcifications in the breast. The aim of the study was to present an open surgical biopsy of the mammographically detected suspicious microcalcifications in a breast, with preoperative wire marking of the lesions and intraoperative specimen radiography, as a reliable and valid procedure.

Material and Methods: The study included 80 female patients underwent surgery because of mammographically detected suspicious microcalcifications. The method of preoperative ultrasound-guided wire marking of a zone of microcalcification was performed in all patients. After wire marking, the control native mammography in ML and CC projections was performed, in order to locate the microcalcifications relative to the wire. In all patients, the extirpation of the suspicious microcalcifications was verified by the specimen radiography.

Results: In the definitive histopathological finding in situ component of ductal carcinoma of the breast was verified in nine (11,25%) examinees. High grade in situ component was verified in eight (10%) examinees and low grade in situ component in one examinee (1,25%). In 11 (13,75%) examinees, the invasive breast cancer with an extensive in situ component up to 50% was verified. In 46 (57,5%) of the examinees, benign, non-proliferative changes were verified, while proliferative changes characterized as premalignant condition (sclerosing adenosis, radial scar and atypical ductal hyperplasia) were verified in 14 (17,5%) examinees. Microcalcifications verified by specimen radiography are completely removed.

Conclusion: Presence of mammographically detected suspicious microcalcifications has a significant predictive value in the early detection of breast cancer. The method of an open surgical biopsy, as an alternative to stereotactic biopsy, is valid in diagnostic of the mammographically suspicious microcalcifications.

Key words: microcalcifications, US guide wire marking, open surgical biopsy, cancer, breast

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Introduction

The breast cancer is the most common malignant neoplasm in women.[1] A mammography gives a possibility of detecting breast cancer in the early stage, when the lesion is non-palpable and when probability of cure is higher.[2] In the modern age the omnipresent and growing concern because of the morbidity of breast cancer resulted in more often recommendations for screening mammography and more intense requests for biopsies of subclinical (non-palpable) lesions.[3] With the introduction of screening mammography, microcalcifications are more often a mammographic characteristic of the minimal invasive breast cancer and ductal in situ cancer (DCIS).[4] Using the spectrometric analysis of the samples with present microcalcifications, the group of researchers from Great Britain indicated the significant correlation between breast cancer and microcalcifications.[5]

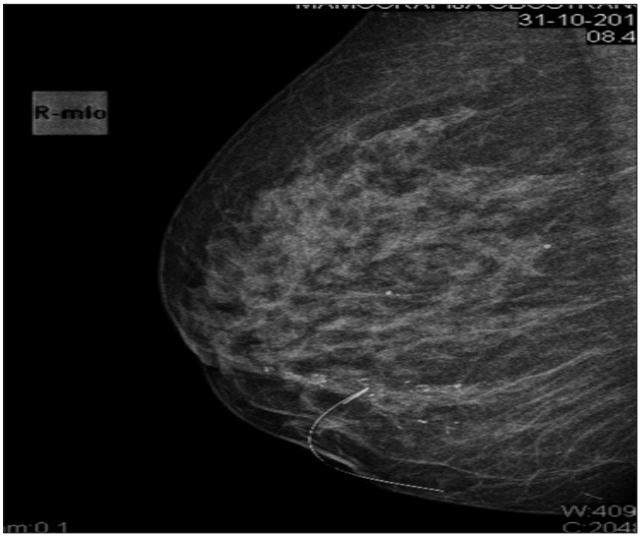
On a morphological basis, we distinguish calcifications of radiologically benign characteristics and calcification of radiologically malignant characteristics. In the group of radiologically suspicious calcifications are amorphous, heterogeneous course, fine pleomorphic, fine linear and fine linear with branching. On distribution basis, we distinguish diffuse, regional, grouped, linear and segmental calcifications.[6] Microcalcifications are the most commonly detected on the mammography and the most of them cannot be visualized with confidence on ultrasound. The lesions detected only on mammography require stereotactically guided biopsy and specimen radiography of the extirpated tissue samples.[7] When performing a biopsy, a radiologist places the clips in order to mark the zone where the biopsy was performed. If a histopathological finding of a biopsy indicates malignancy or suspicious lesion in a breast, a surgical extirpation is indicated and the inserted clips have the purpose of locating a zone of interest for an open surgical biopsy.[8]

However, since the stereotactic biopsy procedure is not affordable to a larger number of patients, because of its price, an alternative to this diagnostic procedure is open surgical biopsy with preoperative wire marking of the lesion (WGL – wire guided localization).[9,10] Extirpation of the suspicious microcalcifications is verified with specimen radiography in order to confirm that the area of the suspicious microcalcifications is removed.[11] This procedure has its limitations too, it is indicated mostly in the suspicious microcalcifications, which are focally localized in a breast. In diffusely spreaded suspicious microcalcifications in a breast, an ultrasound-guided needle biopsy is available, if there is palpable lesion or ultrasonographic signs of suspiciousness in the zone of microcalcifications.[12]

Material and Methods

Retrospective – prospective study. The examined group concist of patients between 35 and 78 years, referred to mammography in the Institute of Clinical Radiology (University Clinical Centre of the Republic of Srpska – UCC RS). Eighty female patients were evaluated. The average age structure of the examinees was 52 years. Digital mammography imaging was performed on GE Senographe Essential FFDM (GE Healthcare, USA). The mammography of both breasts was performed in all the patients in two standard projections (mediolateral oblique and craniocaudal). Mammogram images are analyzed according to the actual BI-RADS (Breast Imaging Reporting and Data System) classification. The study included only those patients who had suspicious microcalcifications on mammogram with or without appearance of a mass classified as BI-RADS 4, by consensus by two radiologists. The method of preoperative ultrasonographically guided wire marking was used in all patients (Mammorep Z, Sterylab, Italy) in the area of microcalcifications.. The patient is in a lying position and the place of planned prick in the skin is disinfected with povidone iodine solution. Wire marking was ultrasound-guided (GE LOGIC 5, GE Healthcare, USA), with ultrasound probe, which was positioned on the skin and visually followed the wire introduction to the expected place of suspicious microcalcifications. After extraction of the guide, the wire is fixed to the skin with adhesive bandage. The local anesthesia was not used. After wire marking, the control mammography is made in mediolateral and craniocaudal projection in order to locate the microcalcifications against the marker (Figure 1).

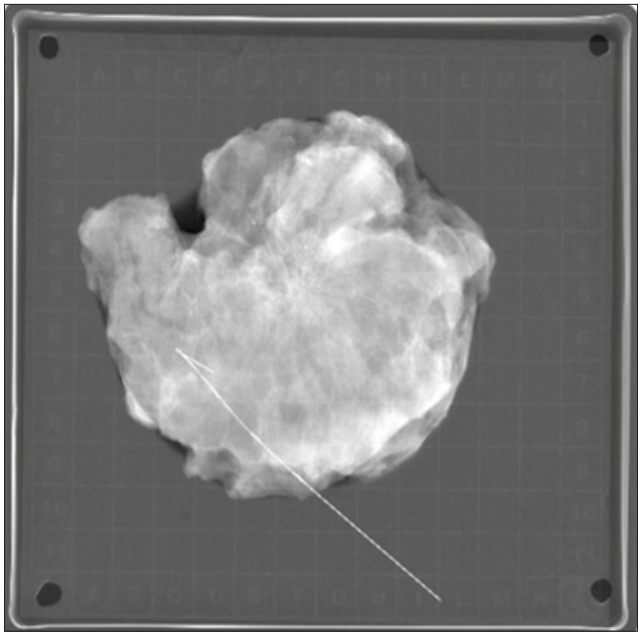
Figure 1. Preoperative mammography



After marking out localization by measuring with

an electronic ruler in PACS (Picture Archiving and Communication System) programme of the position of microcalcifications against the wire, the surgical procedure was performed in general endotracheal anesthesia. Intraoperatively, the extirpated breast segment, with the appropriate wire, marked with the surgical sutures, was sent to specimen radiography. Depending on technical capabilities, the preparation was sent to the specimen radiography (Figure 2) in a container specially intended for it (X-screen, Sterylab, Italy).

Figure 2. Specimen radiography



After confirmation of the suspicious microcalcifications extirpation by specimen mammography, the sample was sent for definitive histopathological analysis, fixed with 10% buffered formalin. Mammography was performed at the Institute for Clinical Radiology of the UCC RS, wire marking and surgical procedure in the Breast Centre of the UCC RS and histopathological verification in the Institute of the Clinical Pathology UCC RS. The Clinical Information System (CIS) was used for collecting the data and for archiving and processing of the radiological images PACS program was used. The data obtained were processed statistically.

Results

The most often localizations of the suspicious microcalcifications in a breast was related to upper lateral quadrant and upper quadrant compound. In 42 (51,22%) examinees the mammographic suspicious microcalcifications were located in that area. Histopathological analysis of the extirpated microcalcifications is shown in the Table 1.

Table 1. Histopathological reports of the breast specimens

No	Specimen	Number/%
1.	Fibrocystic mammary changes	35 (43.75%)
2.	Adenosis gl. mammae	5 (6.25%)
3.	Adenosis sclerosans	11 (13.75%)
4.	Radial scar	3 (3.75%)
5.	Adenosis microglandularis	1 (1.25%)
6.	Papillomatosis	5 (6.25%)
7.	DCIS High grade	8 (10%)
8.	DCIS Low grade	1 (1.25%)
9.	Ca ductale invasivum	9 (11.25%)
10.	Ca lobulare invasivum	1 (1.25%)
11.	Ca tubulolobulare invasivum	1 (1.25%)
	SUMMARY	80 (100%)

Based on the obtained data on the histological character of the excised changes, in 11 (13, 75%) patients, the invasive component of breast cancer was verified. In 9 patients, in situ component of breast cancer was found, in 8 (10%) high grade and in one (1, 25%) low grade component. Histological analysis has shown in 14 (17, 5%) patients the presence of premalignant lesions such as radial scar and adenosis sclerosans. In 46 (57, 5%) patients, the histological analysis has shown the existence of benign lesions. During the procedure, there were no significant complications like infection or haemorrhage. Discomfort in patients during wire placing was minimal. The patients were discharged from hospital from the first to the third postoperative day. In 46 patients, where the benign breast lesion was verified, by the additional radiological control examinations, the presence of suspicious breast lesions were not found. Positive predictive value was 25% and negative predictive value 100%.

Discussion

Diagnosis of breast cancer at an early stage is priceless for the final outcome in the management of patients suffering from this disease. The condition for breast cancer detection at an early stage is an adequate radiological diagnostic. Use of mammography started in 1913 when the surgeon Albert Salomon has shown his research, in which he used radiography of the mastectomy specimen in order to show the tumour spreading into axillary lymphnodes.[13] By introducing

routine mammography examinations during the 1960s and with the development of technical characteristics of the obtained mammography image, the problem how to mark non-palpable breast lesions, for which the indication for a histological check was set, appeared. By beginning of the 1970s, the four doctors of the American hospital, independently from one another, had an idea to mark the non-palpable lesions with wire.[14] Since then and until today, with gradual improvement and upgrade of the marking wire technical characteristics, the marking method of the non-palpable lesions with wire remains one of the standards in breast cancer diagnostic.

Due to the technological development and sensitivity of today's radiology analysis (ultrasound, mammography, MRI), detection of small lesions (<1cm) in breast became possible. In the diagnosis of early breast cancer, this is usually the case of non-palpable breast lesions. Introduction of screening mammography lead to increase in detection of non-palpable breast lesions.[15] Non-palpable lesions also include microcalcifications of suspicious mammographic characteristics. In the screening programs between 10 and 40% women are called because of microcalcifications detection.[16] In that regard, detection and histopathological verification of suspicious microcalcifications, participate in early detection of breast cancer and therefore contribute to long-time survival. The recommended diagnostic method for histopathological verification of the suspicious microcalcifications is stereotactic biopsy.[8,17] This method is more comfortable for patients, the surgical procedure is avoided, as well as post-operative defects on the breast, the recovery is faster and the biopsy is targeted. In the absence of this diagnostic procedure alternative is an open surgical biopsy. The open surgical biopsy has its disadvantages and limitations. In the first place, the patient is exposed to the surgical procedure, which is, per se, because of the possible post-operative complications, one kind of a risk. The open surgical biopsy has its limitations in diffusely spread microcalcifications and voluminous breasts. However, taking all into consideration, the results indicate that the open surgical biopsy, followed by specimen mammography, is a valid diagnostic procedure in histopathological verification of suspicious microcalcifications. In addition, good education and skills of the team which performs the procedure, is necessary. Our results show that, from the total number of the operated patients, in 25% malign in situ and invasive component of breast cancer was verified. The obtained data are compatible with those from the professional literature, which indicate that, in nearly 30% of suspicious microcalcifications, the malignant component of breast cancer is present.[18] In examinees within which the histopathological finding indicated to benign change in the breast, by postoperative radiological follow up, new suspicious changes did not appear.

Conclusion

In circumstances when the procedure of stereotactic biopsy is unavailable, open surgical biopsy, with preoperative wire marking and specimen radiography, is a valid method in diagnostic of mammographic suspicious microcalcifications.

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Otvorena hirurška biopsija u dijagnostici mamografski suspektnih mikrokalcifikata

SAŽETAK

Uvod: Jedan od najranijih znakova karcinoma dojke može biti prisustvo mamografski suspektnih mikrokalcifikata u dojci. Cilj rada je da se otvorena hirurška biopsija mamografski suspektnih mikrokalcifikata u dojci, uz preoperativnu markaciju lezije žicom i intraoperativnu specimen radiografiju, prikaže kao pouzdana i validna procedura.

Materijal i metode: U istraživanju je učestvovalo 80 pacijentkinja kod kojih je sproveden hirurški zahvat zbog mamografski detektovanih suspektnih mikrokalcifikata. Kod svih pacijentkinja korišćena je metoda preoperativnog markiranja žicom zone mikrokalcifikata sa ultrasonografskim navođenjem. Nakon markiranja žicom rađena je kontrolna nativna mamografija u ML i CC projekciji radi lociranja mikrokalcifikata u odnosu na žicu. Kod svih pacijentkinja ekstirpacija suspektnih mikrokalcifikata verifikovana je specimen radiografijom.

Rezultati: U definitivnom histopatološkom nalazu kod devet (11,25%) ispitanica verifikovana je duktalna in situ komponenta karcinoma dojke. U osam (10%) slučajeva verifikovan je visoki gradus (high grade) in situ komponente, u jednom (1,25%) slučaju niski gradus (low grade). Kod 11 (13,75%) ispitanica verifikovan je invazivni karcinom dojke sa prisutnom ekstenzivnom in situ komponentom i do 50%. Kod 46 (57,5%) ispitanica verifikovane su benigne neproliferativne promene, kao i proliferativne promene okarakterisane kao prekanceroze (sklerozirajuća adenoza, radijalni ožiljak i atipična duktalna hiperplazija) kod 14 (17,5%) ispitanica. Mikrokalcifikati su odstranjeni u celosti, što je verifikovano specimen radiografijom.

Zaključak: Prisustvo mamografski suspektnih mikrokalcifikata ima značajnu prediktivnu vrednost u otkrivanju ranog karcinoma dojke. Metoda otvorene hirurške biopsije, kao alternativne metode u odnosu na stereotaksijsku biopsiju, je validna u dijagnostici mamografski suspektnih mikrokalcifikata.

Ključne riječi: mikrokalcifikati, UZ vođeno markiranje žicom, otvorena hirurška biopsija, karcinom, dojka

CASE REPORT

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Advantages of Percutaneous Coronary Intervention in Relation to Medication Therapy in Patients with Stable Angina Pectoris (Three-Wessel Coronary Disease)

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ABSTRACT

Patient, a man, age of 66 years, was admitted to the Internal Department, Interventional Cardiology Department for chest pains by type of stable angina pectoris. CCS II. In ambulatory conditions he was made non-invasive diagnostics, and after a positive ergometric test, a decision was made that the patient be admitted to the catheterization hall for invasive diagnosis and possible percutaneous coronary intervention.

Key words: angina pectoris, coronary disease, percutaneous coronary intervention, interventional cardiology, case report

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Introduction

Three randomized studies compared PCI with medication treatment. The ACME study[1,2] is planned to evaluate whether PCI is better than optimal pharmacological therapy for alleviating angina in patients with the disease of one and two coronary arteries. PCI previously relieved angina more thoroughly than medicament therapy and was associated with better effort and / or less ischemia in the load test.[1] Some early beneficial effects of PCI in patients with single-headed coronary disease have been maintained, which makes it an attractive therapeutic option in such patients.[2] The ACIPO study[3] is targeted to patients with severe daily ischemia. At the 48-hour Holter ECG, patients had an ischemic effort and at least one episode of silent ischaemia. Two years after randomization, total mortality was significantly reduced, from 6.6% in the angina-guided strategy to 4.4% in ischemic strategy and 1.1% in the revascularization strategy.[4] (Recommendations for PCI in the treatment of objective extensive ischaemia: IA). However, in patients with no symptoms or with mild symptoms, the situation is different, with poor probability of improvement with PCI, as demonstrated in the AVERT study.[5,6] After 18 months, 13% of patients in whom aggressively lowered lipids had episodes of ischemia, in conjunction with 21% of patients undergoing planned PCI. This difference was initially statistically significant, but it lost significance in a later analysis. There are two major limitations of AVERT experiment: (I) Comparison of pharmacological therapy and PCI is not adequate, as more aggressive hypolipenic therapy is used in the pharmacological part; stenting was done in only 30%, and restenoses that require re-intervention are more likely to be in the PCI group than in conservatively treated patients. (II) AVERT did not

show the anti-ischemic effect of the statin but showed that statins can prevent acute coronary events. RITA-2 was a randomized experiment in which long-term effects of PCI and conservative (pharmacological) treatment of patients with CAD suitable for another therapeutic option were compared.[7] After a median follow-up of 2.7 years, in 6.3% of patients treated with PCI, myocardial infarction or myocardial infarction occurred, as opposed to 3.3% of patients under medication therapy (P = 0.02). On the other hand, PCI has been associated with greater symptomatic improvement, especially in patients with severe angina. However, RITA-2 can not be applied to today's modern PCI. Only 7.6% of patients received stents. The study did not mention ticlopidine, clopidogrel, or GP IIb/IIIa inhibitors. The meta-analysis of randomized controlled experiments found that PCI could significantly reduce angina compared to pharmacotherapy, although experiments did not include enough patients for an informative assessment of the effect of PCI on myocardial infarction, death, or later revascularization.[8] Regardless of involvement in invasive or pharmacological treatment (study TIME) and the administration of at least two antianginos anti-angina drugs, the long-term survival of patients aged 75 or over, in the class of angina II or higher toward the Canadian Cardiac Society (CCS), was similar. Benefits of both types of treatment in relation to angina alleviation and improvement of quality of life were present, but non-fatal events were more frequent in patients under medical therapy. Regardless of whether patients were catheterized at the beginning or only after failing pharmacotherapy, survival was better when they were revascularized in the first year.[9] Expenses should not be an argument against invasive treatment of elderly patients with chronic angina.[10]

Case Report

Patient, a man, age of 66 years, was admitted to the Internal Department, Interventional Cardiology Department for chest pains by type of stable angina pectoris. CCS II. In ambulatory conditions he was made non-invasive diagnostics, and after a positive ergometric test, a decision was made that the patient be admitted to the catheterization hall for invasive diagnosis and possible percutaneous coronary intervention. EHO heart: Ao root 35 mm, AR 1+, LPK 42 mm, EDD 52 mm, ESD 29 mm, IVS 11 mm, PW 11 mm, EF 60%, MR 1-2 +.

Ergometry: the physical load test was interrupted in the third minute of grade III due to fatigue and angina pain with the achieved SMF. During the test registered ST depression of 3mm in left overdrive and ST elevation in aVR outflow. Earlier it was treated with a mild form of hypertension and hypercholesterolemia. Positive family history.

Finding Coronarography: Right Radial Approach:

LCA: LM: correct deviation, direction, lumen, no stenosis, divides into LAD and LCx. LAD: correct deviation, direction, proximal in the long segment narrowed by tubular stenosis of about 95%, distal stenosis about 50%. LCx: the correct deviation, direction, gives OM1 a branchless limb, the OM2 branch that is proximal narrowed about 60-70% (tandem lesion) and the OM3 (PD) branch is proximal subcoded to 99%. (Figure 1). RCA: correct deviation, direction, lumen, no stenosis, minor. (Figure 2). (LCA-left coronary artery, LAD-anterior descending artery, LCx-circumflex artery, OM-obtuse marginal artery, PD-posterior descending, RCA-right coronary artery.

Figure 1. RAO CAUD (subcooled LAD with stenoses on OM2 and OM3 branches)

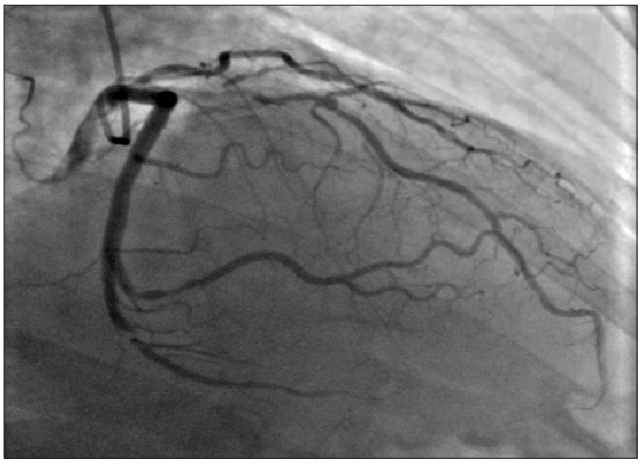
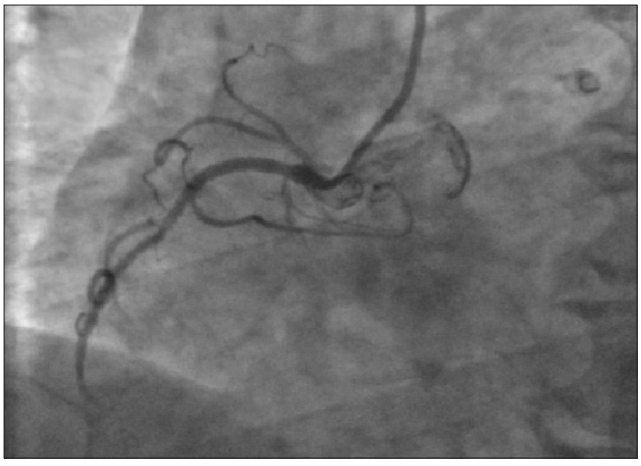


Figure 2. LAO CAUD (Right coronary artery minor)



PCI SYNTAX Score II: 23.0; PCI 4 year mortality 3.8%. CABG SYNTAX Score II: 25,3; CABG 4 year mortality 4.6%.

Figure 3. Implanted stent DES Orsiro 3.0x35mm and BMS 3,5x15mm ower-lap technique with stenoses on OM2 and OM3 branches

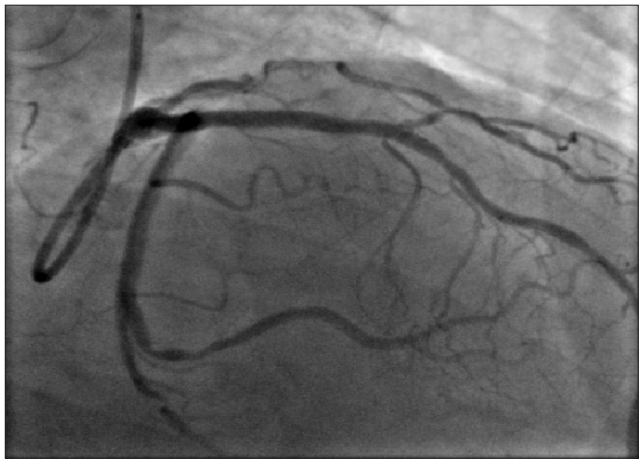
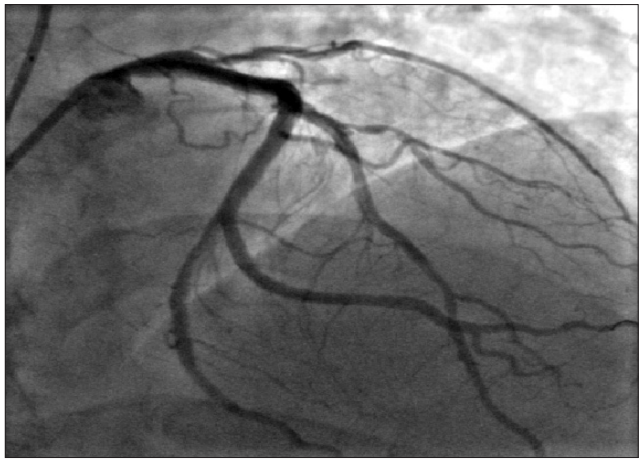


Figure 4. Implanted stents BMS Integrity 2.5x18mm in OM3 (PD) branch and stent DES Resolute integrity 2.5x22mm in the direction of the OM2 branch



Percutaneous coronary intervention of LAD, OM2 and OM3: given by Heparin a 8000 i.j.i.a. Installed guiding catheter EBU 3.75 from 6fr to ostium LCA.

PCI LAD: Placed guidwire Runtrough floppy in the direction of Dg branch as protection and guidwire BMW to the periphery of LAD. Stenosis predilation, SC Pantera balloon 2,0x20mm insufflation to 14atm and balloon NC Sprinter 2,5x15mm insufflation up to 16atm. Implanted stent DES Orsiro 3.0x35mm insufflation to 14 atm. Proximally implanted stent ower lap by BMS Integrity 3.5x15mm insufflation to 16atm. After that, POT technique was made, balloon of BMS stent insufflation to 18atm and postdilatation of ower lap with insufflation of up to 18atm. (Figure 3).

PCI OM3: Replaced guidwire BMW in PD direction and Direct technique implanted BMS Integrity stent 2,5x18mm insufflation to 18atm.

PCI OM2: Placed guidwire Runtrough floppy in the direction of OM2 branch and Direct technique implanted stent DES Resolute integrity 2.5x22mm insufflation to 16atm. Final result without residual stenosis, without dissection with TIMI flow III. (Figure 4).

Conclusion

The patient was admitted to the catheterization hall due to chest pains by the type of stable angina pectoris with a positive physical fatigue test. After percutaneous coronary intervention, the patient was discharged to a home without symptoms and electrocardiographic signs of ischemia with a proposal to continue treatment with medication (dual antiaggregation therapy and high dose statins). At the checkup, after a month and six months, the patient still has no problems with the proposal to continue the prescribed therapy for one year. The aim of the case is to indicate the significance of percutaneous coronary intervention in patients with stable angina pectoris versus drug therapy. The procedure must be gradual and carefully planned. Conclusion based on the literature and the case itself, a patient with a clinical picture has stable angina pectoris and well-performed non-invasive diagnostics, they discover with significant coronary artery stenosis. Consequently, the performance of PCIs in such patients can be considered as a more effective treatment method than a medical treatment due to a reduction in the symptoms itself and the development of consequent ischemic cardiac insufficiency.

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Prednosti perkutane koronarne intervencije u odnosu na medikamentoznu terapiju kod pacijenata sa stabilnom anginom pektoris (trosudovna koronarna bolest)

SAŽETAK

Uvod: Cilj ovog rada je prikazati postupak perkutane koronarne intervencije kod pacijenata sa stabilnom anginom pektoris i njene prednosti, s obzirom da se ne preporučuje rutinska PCI kod pacijenata sa stabilnom anginom prema važećim preporukama, dobijenih na osnovu velikih radomizovanih studija, koje će kroz rad biti opisane.

Prikaz slučaja: U Pacijent, muškarac, životne dobi od 66 godina, primljen je na Interno odelenje, odsek za Interventnu kardiologiju zbog bolova u grudima po tipu stabilne angine pektoris. CCS II. U ambulantnim uslovima mu je učinjena neinzvazivna dijagnostika, te nakon pozitivnog ergometrijskog testa, donešena je odluka da se uradi invazivna dijagnostika i eventualna PCI. PCI SYNTAX Score II: 23,0; PCI četvorogodišnji mortalitet 3,8%. CABG SYNTAX Score II: 25,3; CABG četvorogodišnji mortalitet 4,6%. Koronarografija: LCA: LM: pravilnog odstupa, pravca, lumena, bez stenoza, račva se na LAD i LCx. LAD: pravilnog odstupa, pravca, proksimalno u dužem segmentu sužena tubularnom stenozom oko 95%, distalno stenoza oko 50%. LCx: pravilnog odstupa, pravca, daje OM1 granu koja je bez suženja, OM2 granu koja je proksimalno sužena oko 60-70% (tandem lezija) i OM3 (PD) grana je proksimalno subokludirana 99%. RCA: bez stenoza, minorna. PCI LAD: Implantiran stent DES Orsiro 3,0x35mm insuflacijom do 14 atm. Proksimalno implantiran stent ower lap tehnikom BMS Integrity 3,5x15mm insuflacijom do 16atm. Nakon toga, urađen POT tehnika, balonom od BMS stenta insuflacijom do 18atm i postdilatacija ower lap-a insuflacijom do 18atm. PCI OM3: Replasiran guidwire BMW u pravcu PD grane i Direct tehnikom implantiran stent BMS Integrity 2,5x18mm insuflacijom do 18atm. PCI OM2: Plasiran guidwire Runtrough floppy u pravcu OM2 grane i Direct tehnikom implaniran stent DES Resolute integrity 2,5x22mm insuflacijom do 16atm. (LCA-leva koronarna arterija, LAD-prednja descendentna arterija, LCx-cirkumfleksna arterija, OM- optuzna marginalna arterija, PD- zadnja descedentna arterija, RCA-desna koronarna arterija).

Zaključak: Procedura mora biti postupna, pažljivo planirana i da tek nakon inicijalne i dobre neinvazivne dijagnostike, se treba pristupiti odluci o perkutanoj koronarnoj intervenciji. Značajan stepen stenoza na koronarnim arterijama i tegobe koje pacijent ima su presudne u odluci o izvođenju PCI. Ako se pažljivo izvodi, PCI se i dalje može smatrati dragocenom tehnikom kod odabranih pacijenata u odnosu na samu medikamentoznu terapiju.

Ključne riječi: angina pektoris stabilis, perkutana koronarna intervencija, medikamentozna terapija

CASE REPORT

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Acute Poisoning with Herbicide Glyphosate

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ABSTRACT

Glyphosate is the most common used organophosphorus herbicide which most probably inhibits oxidative phosphorylation without leading to the inhibition of esterases. Glyphosate poisoning is mostly the consequence of the synergistic effect of an active substance and surfactant. There is a case of 42-year-old patient who worked on weed spraying with glyphosate, with hand sprinkler. Symptoms of the acute poisoning such as weakness, sweating, nausea, vomiting and stomach ache were visible right after the working period. With biochemical analysis increased activity of the enzymes AST, ALT and y-GT were diagnosed and sanated after aborting an expositions in the period of six months and treatment. In this shown case poisoning was caused during applying herbicides without proper handling with the herbicide and also because of non-compliance of measures in safety and health at work. It is very clear that this is a case of acute poisoning with pesticides which ended with no consequences and was declared as work injury.

Key words: glyphosate, acute poisoning, enzymes, safety and health

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Introduction

Glyphosate (N-phosphonomethylglycine) is a non-selective (total) organophosphorus herbicide, with wide spectrum of action to suppress undesirable vegetation on agricultural and non-agricultural soil and is one of the most widely used herbicides worldwide. It is considered to be a minimum toxic for humans.[1] It does not lead to esterase inhibition, it is considered that the mechanism of glyphosate toxicity in mammals is to prevent oxidative phosphorylation.[2] Acute oral lethal dose LD50 for rats is> 4320 mg/kg, dermal LD50 is> 2 g/kg and the inhaled lethal concentration 50 is> 4.43 mg/l.[3] After oral ingestion of glyphosate 30-36% is absorbed, maximum concentrations occur in tissues 6 hours after poisoning, undergoes with small metabolic processes and excretes largely unchanged in feces and secondary to the urine. Gastrointestinal symptoms are most common manifestations after oral poisoning. It exacerbates gastrointestinal tract erosion, difficulty swallowing and gastrointestinal bleeding. Eye and skin irritation occurs occasionally when exposured through the skin. Ingestion of the fog when spraying can cause irritation in the mouth, nose, eyes and throat. Severe poisoning causes dehydration, hypotension, pneumonitis, oliguria, changes in consciousness levels, hepatic dysfunction, acidosis, hypercalemia and dysrhythmia.[4,5] Patients developing acute renal failure, hypercalemia, pulmonary edema and metabolic acidosis are more likely to die.[6] However, in commercial products , glyphosate is dissolved in surfactants, substances added to herbicides to enhance their resorption and which can significantly contribute to the toxicity of the products.[7] Most commonly,

isopropylammonium (IPA) and polyoxyethyleneamine (POEA) are used. This is particularly true of glyphosate-based preparations, which have proven to be more toxic than individual components.[8,9] Therefore, it is more appropriate in the poisoning of these formulations as a toxic agent to name glyphosate surfactant than glyphosate. The acute toxicity of herbicides containing glyphosate and surfactant was first described in the medical literature by Japanese authors who published a series of 56 cases of self-destruction, including nine deaths.[10] By their estimates, the lethal dose of the peroral injected preparation was about 200 mL. Considering the low acute toxicity of glyphosate, this group of authors argued that polyoxyethyleneamine toxicity (POEA) was a surfactant in most products.[10] Based on published cases, the symptoms and signs of poisoning containing glyphosate and surfactant preparations included abdominal pain, vomiting, stagnant changes in the lungs, pneumonia, acute lung injury, somnolence-to-coma awareness disorder, haemolysis, hypotension, renal insufficiency, shock, erosion of the gastrointestinal tract and larinx damage.[11,12]

There is no antidote for glyphosate, and treatment is both supportive and symptomatic. The basis for systemic toxicity is decontamination and aggressive symptomatic therapy. Gastric emptying or active coal may be applied to patients <1 h after ingestion and have no severe irritation or erosion.

The aim

The aim of this work is to point out the clinical picture of acute glyphosate poisoning and the importance of preventative measures and measures of safety and health at work.

Case report

There is shown a case of a 42-year-old male, employed as a cleaner of the streets and green areas. He has worked for 9 months until this case occurred. Low-skilled worker, finished elementary school. According to anamnestic data, alcohol consumes "moderately". On May 27th, he worked on spraying the weeds on green areas beside the public roads, with the manually sprayer worn on his back. Spraying mixture was made by himself by diluting the herbicide glyphosate from the plastic bottle with water. He usually used a work suit, shoes, and had gloves available. He did not have protective glasses, face visor, and mask. He worked from 08 to 14 o'clock in the warm and sunny weather, with no significant wind. Together with him were two more experienced workers who had no symptoms of poisoning. During the work he had a half-hour meal break. The meal was eaten at the workplace without hand washing. After working hours he felt the first problems in the form of exhaustion, weakness in his hands and feet, nausea, anxiety, and appetite loss. The next day, besides the aforementioned problems and vomiting in the morning, he went to work and continued to work the same job at another location from 08:00 to 13:30 when he stopped because he felt the general weakness, could not stand on his feet, vomiting, stomach pain, headache, sweating, and reports to Emergency Medical Assistance when a diagnosis is made: T47 (poisoning by means primarily acting on the gastrointestinal tract – Intoxicatio instrumentis systema gastrointenstinale primum afficientibus); T60 (Toxic effect of pesticides - Effectus pesticidorum toxicus) and A05 (Other food poisoning caused by bacteria - Intoxicationes alimentariae bacteriales aliae). From the Emergency medical help he is sent to the Intern Clinic. In the admissions of the Internal Clinic was examined, not hospitalized, given symptomatic therapy and diagnosed: Intoxicatio cum glyphosat susp. It was appointed for a control with certain biochemical laboratory findings. No consultation of the medicine work was requested.

A check-up of the gastroenterologist at the International Clinic was carried out the following day, on the basis of clinical examination and biochemical findings suggesting an increase in enzymatic activity: aspartate - aminotransferase (AST) 125U / L, alanine – aminotransferase (ALT) 130U / L, gamma glutamyl transferase (γ-GT) 926 U / L, and urinary system infection, diagnoses: Laesio hepatis. Infectio tr. urinarii. Ultrasound examination (UZV) diagnosed enlarged liver.

The next gastroenterologist's check on June 11th of the same year, reported a slight decrease in enzymatic activity. In biochemical findings of the 18th of the same year, enzyme findings related to liver function improved. He was on a medical examination on July 4th the same year, 37 days after the scene. In the medicine of work it was noted that acute poisoning was performed with glyphosphate, a herbicide from the group of organophosphorus pesticides. The assumption is that the path of entry was the digestive (per os) and respiratory system. The patient was monitored, the values of the enzyme were normalized until September, except γ-GT. At the beginning of November of the same year, all findings were normalized,liver growth was sanated and the patient is returned to work.

Discussion

According to the World Health Organization (WHO) and the Food and Agriculture Organization (FAO), as well as some authors, early symptoms of glyphosate poisoning include vomiting, diarrhea, and other symptoms similar

of flu.[4] Poisoning may occur with absorption through the skin or through the mucous membrane. The individual may have rash or itching, redness, where direct skin contact has occurred. If swallowed, poisoning can mimic food poisoning and cause stomach cramps and possible throat irritation.4 Authors from Serbia described severe poisoning, most likely with surfactant, with neurological sequelae and lethal outcome.[5,13] The clinical picture of the case described corresponds to the known and described symptom of the Glyphosate poisoning. In the case of the presented patient, the most significant manifestations of poisoning were the increase in enzyme activities of AST, ALT and γ-GT. Increased liver enzymes and liver damage, while experimental mice poisoned with glyphosate were alleged by Egyptian authors.[14] Gastrointestinal disorders and liver injury, as well as renal disease, are also cited by other authors.[4]

By inspecting the health card, there is no evidence of habitual consumption of alcohol, or any other means of dependence or liver damage of another etiology, as confirmed by laboratory findings (hepatitis markers). The worker was temporarily unable to work until the clinical and liver enzyme finds were repaired, about 6 months when he returned to work. It has been established in the medical profession that this is not a professional illness, but a work injury.

The following factors have also been noted that have had a significant impact on the aforementioned event and resulted in acute poisoning: A workplace was not identified as a workplace with an increased risk, the worker was not trained to perform work safely and was not educated about the harmful effects of chemical substances used on the job, nor on the protection measures. When preparing the substance for the application, no measures for safe and healthy work, as well as during the application itself, are respected. Workers are not prohibited from consuming food and beverages during work, do not have to wash their hands for eating during meals during breaks, nor are they educated about the importance of personal hygiene in prevention, nor have they been provided with adequate personal protective equipment. No previous review was performed and no selection of workers for this job was performed according to health conditions.

Conclusion

In the case described, poisoning occurred during the application of the herbicide due to improper handling of the herbicide and non-compliance with safety and health at work. From the presented case it is apparent that poisoning with glyphosate pesticide has caused general weakness, headache, sweating, stomach pain, nausea, vomiting and liver damage, which has been remedied for 6 months without any consequences and is perceived as a work injury.

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Akutno trovanje glifosatom

SAŽETAK

Uvod: Glifosat ja najčešće korišćeni organofosforni herbicid, koji ne dovodi do inhibicije esteraza, već najvjerovatnije onemogućava oksidativnu fosforilaciju. Trovanje glifosatom je najčešće posljedica sinergičnog dejstva aktivne materije i surfaktanta. Prikazan je slučaj pacijenta starog 42 godine koji je radio na prskanju korova glifosatom, ručnom prskalicom. Simptomi akutnog trovanja su se ispoljili neposredno nakon završetka radnog dana u vidu slabosti, znojenja, muke, povraćanja i bolova u stomaku. Biohemijskim nalazima utvrđene su povećane aktivnosti enzima AST, ALT i γ- GT koje su se sanirale nakon prekida ekspozicije u trajanju od 6 mjeseci i liječenja. U prikazanom slučaju do trovanja je došlo prilikom primjene herbicida usljed nepravilnog rukovanja herbicidom i zbog nepridržavanja mjera bezbjednosti i zdravlja na radu. Iz prikazanog slučaja je očigledno da se radilo o akutnom trovanju pesticidom, koje se završilo bez posljedica, a koje je shvaćeno kao povreda na radu.

Ključne riječi: glifosat, akutno trovanje, enzimi, bezbjednost i zdravlje.

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De Lacey G, Record C, Wade J. How accurate are quotations and references in medical journals. BMJ 1985; 291:884-6.

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International Society of Scientometrics and Informatics Web site. Available at: http://www.issi-society.info Accessed March 20, 2012.

Lock SP. Journalology: are the quotes needed? CBE Views. 1989:1257-9. Available at: http://garfi eld.libraryupenn. edu/ essays/v13p019y1990.pdf. Accessed April 25, 2012.

Review article

Review articles are written by individuals who have studied a particular subject or area extensively, and who are considered experts. For these reviews, the word count may not exceed 2.500 words, excluding references and abstract. The manuscript may have up to 4 tables or illustrations, and as many as 50 references.

Case report

Case reports are most likely to be published if they describe any of the following: an unreported drug side effects (adverse or benefi cial), 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, fi ndings 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.

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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 guardian must be obtained before submission.

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 guardian. The cover letter from the corresponding author should state that written consent was obtained.

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Solutions for various clinical problems, including certain clinical studies, should include the following sections: Abstract, Introduction, Methods or Case(s) Presentation, up to four tables or illustrations, Discussion, References

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