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ORIGINAL ARTICLE

Secondary Failure of Oral Therapy in Patients With Type 2 Diabetes - How To Overcome It?

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Abstract

Background/Aim: Secondary failure of oral therapy occurs after a long period of successful use of oral antidiabetic drugs. The exact mechanism of its occurrence is not known. Recent data suggest heterogeneity of this phenomenon, analogous that of type 2 diabetes pathogenesis. Research objective was to assess glucoregulation and insulin secretory function before, three months after the use of insulin therapy and three months after the exclusion and re-introduction of oral antidiabetic therapy.
Methods: Forty-nine patients with unsatisfactory glycaemic control were selected and insulin therapy in four daily doses (basal-bolus regimen) was subsequently initiated. Glycaemic regulation and beta cell function (C-peptide and insulinemia) were monitored at three time points: before starting insulin therapy, three months after initiating insulin and three months after discontinuing insulin and resuming the previously used oral antidiabetics.
Results: After the introduction of insulin therapy, there was a significant improvement in glycaemic regulation parameters ($p < 0.001$). Improvements in beta-cell function and reductions in insulin resistance were confirmed during the period after insulin therapy ($p < 0.001$). However, a certain deterioration in these parameters was observed following the discontinuation of insulin therapy. Additionally, there was a slight decrease in C-peptide and an increase in insulinemia, though these changes were not statistically significant.
Conclusion: Application of intensified insulin therapy for three months leads to improvement of glucoregulation and partial recovery of the secretory function of the endocrine pancreas. The reintroduction of oral antidiabetic therapy led to a slight worsening of the observed parameters, although this change was not statistically significant.

Key words: Pharmaceutics; Therapy; Insulin; Failure; Diabetes mellitus type 2; Treatment switching; Administration, oral.

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Introduction

Secondary failure (SF) of oral therapy in patients with type 2 diabetes is defined as the absence of a favourable response to oral antidiabetic therapy that was effective in the previous period.[1] It is observed that approximately 50 % of patients will experience SF within the first three years of treatment and this rate increases to 75 % after 10 years of diabetes duration. It is more prevalent in non-obese patients with a rate of 6 % per year, compared to 1 % per year incidence in obese patients.

Unsatisfactory glucoregulation as a consequence of increased hepatic glucose production, followed by peripheral glucose metabolism disorder and insulin deficiency is cited as the dominant cause.[2, 3] Multiple linear regression analyses indicate that marked insulin deficiency (12.6 %), increased hepatic glucose production (26.1 %) and impaired glucose metabolism (17.3 %) could explain the cause of this clinical phenomenon in only 56 % of patients. Recent research suggests that this condition exhibits significant heterogeneity, analogous to the heterogeneity of the pathogenesis of type 2 diabetes. Thus, it can be considered logical that in non-obese patients it occurs predominantly due to the deterioration of the insulin secretory function as a consequence of the "depletion" of beta cells, in which the effect of long-term hyperglycaemia is certainly important. In contrast, the dominant cause in obese patients may be the worsening of already pronounced insulin resistance.[4, 5]

The influence of glucotoxicity on the manifestation of this phenomenon is of great importance.[6] Hyperglycaemia becomes an equally important factor in the pathogenetic events of type 2 diabetes.[7, 8] Once hyperglycaemia is established, it becomes a significant factor in the pathogenetic processes of diabetes, thereby contributing to the development of this clinical phenomenon. Thus, hyperglycaemia, viewed not only as a consequence but also as a cause of metabolic destabilisation, represents a target suitable for therapeutic interventions aimed at interrupting the vicious cycle in which hyperglycaemia creates new and higher hyperglycaemia.[9, 10]

In the treatment of those patients, several insulin administration regimens are available.[11] Intensive insulin therapy cannot be considered a rational choice mainly due to the fact that another significant aspect of the dilemma regarding the use of insulin therapy in this group of patients is its atherogenic and mitogenic effects.[12] Precisely because of this, the application of insulin therapy in a limited period of time is gaining more and more importance with the aim of eliminating glucose toxicity.[13] Intermittent insulin therapy aims to normalise blood glucose levels and partially reverse underlying pathophysiological pathways by addressing glucose toxicity.[14, 15] The potential reversibility of fundamental pathophysiological pathways in type 2 diabetes is a key consideration for the success of this therapeutic regimen.[14, 16]

A general hypothesis was presented that the application of insulin therapy, in a period of three months, leads to an improvement of glucoregulation and a partial recovery of the secretory function of insulin.[10, 17] Different regimens of mono-insulin and combined therapy show different effectiveness in this case.[18] Therefore, this research focused on examining the immediate and lasting effects of short-term intensified mono-insulin therapy on glucose regulation and insulin secretory function.

Methods

Prospective research was conducted over six-month period. It was conducted in two phases and included 49 patients with type 2 diabetes mellitus and SF of oral antidiabetic therapy. In the first phase of the investigation, insulin therapy was started for three months, after which the acute effects of the therapy on the observed parameters were assessed.

The second phase also lasted for three months, during which patients were transitioned back to their previous oral therapy, the regimen in use at the time when SF was diagnosed. At the end of this phase, residual effects of short-term intensified insulin therapy were evaluated. Glucoregulation was estimated according to daily self-assessment profiles, fasting glycaemia and postprandial glycaemia. The insulin secretory function was assessed based on insulin and C-peptide levels, measured at three distinct time points. At the end of study, based on the obtained parameters, the possibility of achieving re-sensitivity to oral therapy, ie the possibility of overcoming SF of oral therapy, was evaluated.

Results

Glucoregulation

At the end of the first phase of the research, ie three months in which the patients were treated with intensified insulin therapy, all parameters of glucoregulation were obtained, same as at the beginning of the research, when SF of oral therapy was verified. After the introduction of insulin therapy, there was a significant improvement in all parameters of glycaemic regulation, improve-

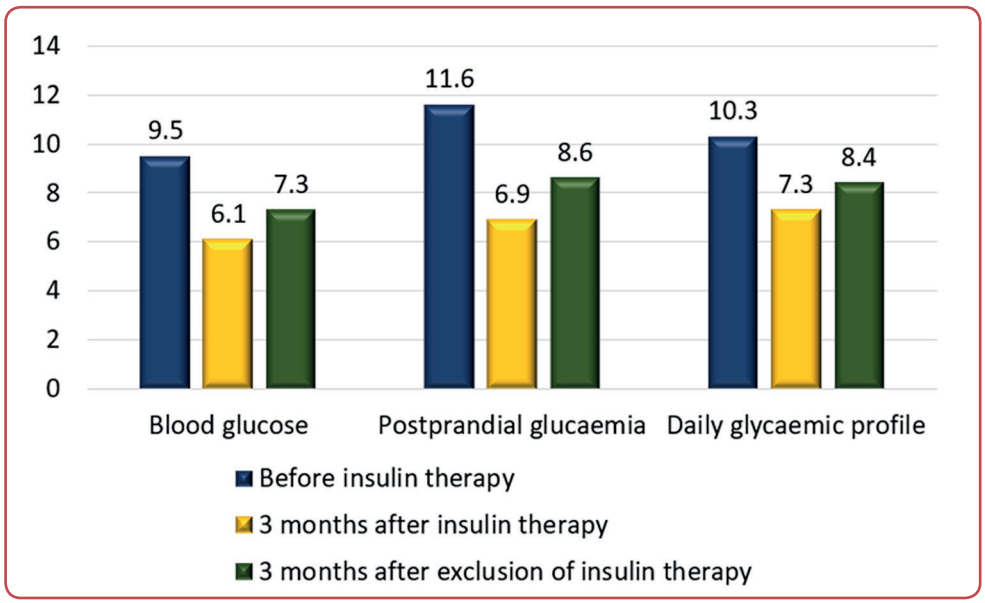

Figure 1: Glucoregulation parameters in all three follow-up times

ment of beta cell function and reduction of insulin resistance (acute effects) ($p < 0.001$). (Figure 1). Three months after the re-introduction of oral therapy, all parameters of glucoregulation were reassessed. The results showed that there was a certain deterioration of these parameters, without statistical significance (Figure 1).

Insulin secretory function

In addition to glycaemic control, the insulin secretory function of the endocrine pancreas was also evaluated in the patients included in this study. Plasma concentrations of C-peptide and insulin were measured, simultaneously with the determination of blood glucose levels. Following insulin therapy, a reduction in basal insulinemia was observed in the studied group (9.17 vs 11.46) (Figure 2). This decrease can be regarded as a favourable outcome of the therapy, particularly when considered in the context of the existing glycaemic levels. Given that these lower values of insulinemia occurred with significantly lower glycaemic levels than before insulin therapy, it can be concluded that this was a marker of insulin secretory recovery of beta cells.

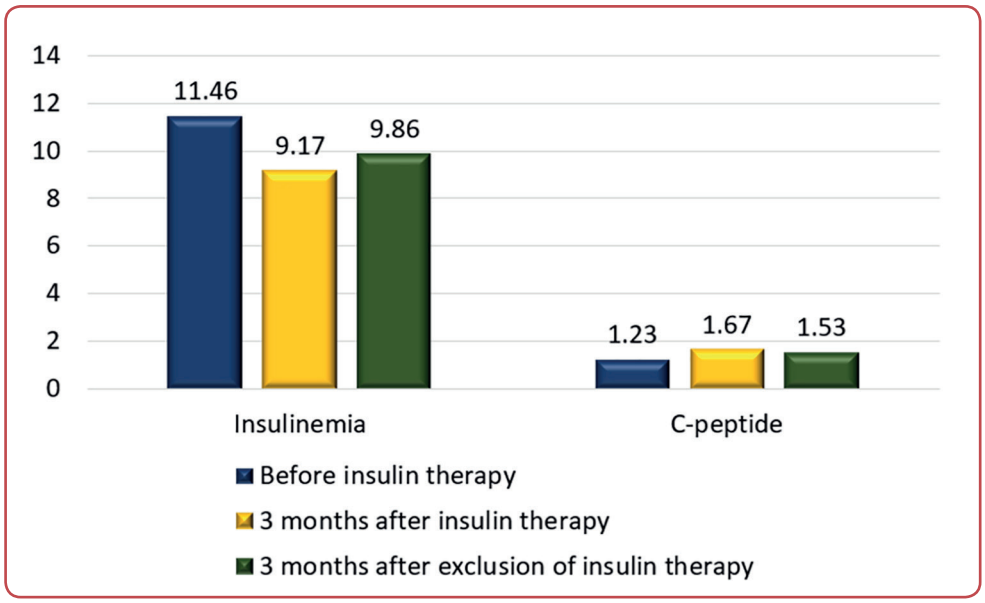

Figure 2: Basal values of insulin secretory function parameters

After the introduction of insulin therapy, an increase in basal C-peptide values was observed (1.67 vs 1.23). This increase in basal C-peptide values after insulin therapy was of great importance, especially when considered in the context of significantly lower glycaemia (Figure 2). However, after the re-inclusion of the previous oral therapy, there was a certain worsening of the observed parameters: C-peptide (1.53 vs 1.67) and insulinemia (9.17 vs. 9.86) (Figure 2).

Discussion

If it is not associated with the evidently present criteria for the use of permanent insulin therapy, the moment of occurrence of SF of oral therapy is particularly significant from the clinical aspect of therapeutic dilemmas in diabetes mellitus type 2.[19] Recent evidence suggests that the effects of glucose toxicity may be reversible. Namely, diabetes mellitus type 2 is primarily a disease that is based on functional disorders and structural disorders to less extent, so there is a reasonable possibility of reversion (up to a certain degree, of course) of pathophysiological pathways. Based on these facts, strict metabolic control gains importance. It has been proven, however, that achieving strict metabolic control in type 2 diabetes requires the use of higher insulin doses, which can result in pronounced hyperinsulinemia, unwanted weight gain, accelerated atherogenesis and hypertension. These findings are the cause of daily dilemmas encountered in diabetology practice.

The introduction of permanent insulin therapy is certainly the treatment of choice in patients who are evidently insulin deficient.[20] A short-term regimen of insulin therapy can potentially improve insulin secretory function and reduce insulin resistance by addressing glucose toxicity, without necessarily leading to the onset of insulin-related side effects.[21] This has led to an increased interest in insulin therapy for a limited period of time, mainly in order to stabilise glycaemia and attempt to partially reverse the underlying pathophysiological pathways by reversing glucose toxicity.[22]

In 1984 Andrews et al presented findings from a study involving 13 obese patients with type 2 diabetes which demonstrated that one month of insulin therapy resulted in a significant improvement in insulin secretion function, with an increase of up to 2.5 times, as well as enhanced insulin action.[23] In his research, Campos highlights the negative effects of chronic exposure of beta cells to high glucose concentrations, which impair insulin response and increase insulin resistance.[24]

The application of insulin therapy in presented study lasted for three months. This time period was chosen based on previously published studies on the effectiveness of different periods of insulin therapy in patients with type 2 diabetes.[25] There are differences in the duration of therapy in accordance with the success in achieving the desired acute and residual effects, as well as differences in the published results of different authors.[26] In presented subjects, the effect of three-month insulin therapy on all parameters of glucoregulation was satisfactory. When these parameters are considered in the context of lower current blood glucose levels, then a significant recovery of endogenous pancreatic function can be derived.

An evident increase in basal C-peptide values and a decrease in basal insulinemia can be a logical consequence of the drop in morning glycaemia and reduced glucose stimulation. It is important to point out that in presented subjects, satisfactory glucoregulation was achieved with moderate doses of insulin (0.4 units/kg of body weight) and minimal weight gain. The next objective of study was to assess the lasting effects of short-term mono-insulin therapy. The term residual effects refers to residual effects on glucoregulation and insulin secretory function after the re-introduction of oral therapy.

After three months of insulin therapy and re-introduction of the previous anti-diabetes therapy, a certain deterioration of insulin secretory function was observed, while there were no significant changes in insulinemia values. Therefore, re-introduction of oral therapy led to a slight deterioration of glucoregulation and secretory function of insulin. However, in this "post-insulin" period (three months after discontinuing insulin therapy), all metabolic parameters showed a significant improvement compared to the pre-insulin period.

Conclusion

Application of intensified insulin therapy for three months led to improvement of glucoregulation and partial recovery of the secretory function of the endocrine pancreas. The reintroduction of oral antidiabetic therapy led to a slight worsening of the observed parameters, although this change was not statistically significant.

Ethics

The study was approved by the Ethics Committee of the University Clinical Centre of the Republic of Srpska, decision number 01-19-268-2/24, dated 16 July 2024.

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None.

Conflicts of interest

The authors declare that there is no conflict of interest.

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Data access

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

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