Original article

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INSULIN THERAPY INITIATION IN A PATIENT WITH TYPE 2 DIABETES IN EVERDAY CLINICAL PRACTICE: IS THERE A DELAY?

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In everyday clinical practice, there is a large number of patients with poorly regulated type 2 diabetes (T2D), which contributes to the development of chronic complications of diabetes. Delayed initiation of insulin therapy in T2D is a particularly significant cause of poor long-term glucoregulation. There are various reasons for this delay, however, in Serbia as well as in Niš, the center of south Serbia, there is no enough data available. The present study was conducted in order to establish whether there was a delay in initiating insulin therapy in Niš, how long it was delayed in comparison to recommendations and experiences of the others, what was glucoregulation like six months prior to initiation of insulin therapy and whether the insulin therapy should have been initiated at that time.

According to the conducted study, at the time of initiation of insulin therapy, HbA1c was 10.51%, which was significantly higher in relation to other comparable studies. The delay can be considered to be at least 6 months, because at that time HbA1c was 9.63%, and all the criteria for initiation of insulin therapy were met.

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Key words: *type 2 diabetes, insulin therapy initiation, HbA1c, delay*

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Introduction

Diabetes related chronic complications are one of the most important factors that have impact on shortening of life expectancy in people with diabetes, as well as the deterioration of the quality of life (1-4).

The two largest and most significant diabetes studies, UKPDS (5-7) and DCCT (8), have unequivocally shown that good glucoregulation is directly related to the reduction especially of microvascular complications (diabetic retinopathy, diabetic polyneuropathy and diabetic nephropathy), but also to reduction of macrovascular complications and death (8, 9).

In order to have more successful type 2 diabetes management, referent scientific organizations have set HbA1c targets to be below 7% for most of patients, but according to the individual approach, the target can be even lower, between 6.5-8% (9-12).

In everyday clinical practice however, there is a large number of patients with poorly regulated type 2 diabetes, which goes in favor of development of chronic complications of diabetes, i.e. comorbidity. Late start of insulin therapy in type 2 diabetes is a great challenge and a great problem. There are various reasons behind, but basically, it is about insufficient education of both patients and doctors (13-18).

Availability of insulin initiation data in Serbia is quite poor, as well as the answer to the question whether the therapy could have been started earlier.

Research objectives

In accordance with the above mentioned data and performed review of so far available literature, the following research objectives have been set:

1. To examine insulin therapy initiation timeframe in people with type 2 diabetes in relation to glucoregulation.
2. To examine the patient's condition 6 months before insulin therapy introduction, especially in relation to glucoregulation.

Methods and patients

This study was a prospective-retrospective research that included 70 patients with type 2 diabetes treated at the Clinic for Endocrinology, Diabetes and Metabolic Diseases KC Niš in the year 2015.

The study included 40 years old patients and older, with a clinically confirmed diagnosis of type 2 diabetes, at least one year before switching to insulin therapy.

The study included anamnestic and clinical data analysis according to predefined research protocol: at the time of insulin therapy introduction, 6 months before and 6 months after.

All patients were informed in details about the study. Anamnestic data were obtained by a survey questionnaire. Two survey questionnaires (Appendix 10.1 and 10.2) were used throughout the study, and the clinical trial protocol 10.3 was divided into two time intervals:

- Clinical trial protocol 1, which refers to the condition at the time of insulin therapy introduction (Appendix 10.3.1);
- Clinical trial protocol 2, which refers to the patient's condition 6 months before insulin therapy introduction (Appendix 10.3.2).

Statistical data analysis was performed with the SPSS 15.0 software package. Data analysis results are presented in tables and graphs.

Continuous variables are represented by mean values and standard deviations (X ± SD) and medians as a measure of central tendency (Me). Category variables are given as absolute numbers and percentages.

Results

The study included 70 subjects with an average age of 60.97 ± 9.83 years, with a median of 60 years.

Out of the total number of participants, 29 (41.43%) patients were male and 41 (58.57%) were female (Table 1). Patients' age structure is shown in the table.

Female participants were slightly older than the males, but statistically not significant.

The average DM duration was 11.11 ± 6.31 years, and the median duration was 10 years (Table 2).

Table 1. Patients'age/sex characteristics

	Age (years)		
	X ±	SD	(Me)
Male	58,55 ±	9.12	(58.00)
Female	62.68 ±	10.06	(62.00)
Total	60.97 ±	9.83	(6000)

Table 2. DM duration

	DM duration (years)		
	X ±	SD	(Me)
Male	10.34 ±	5.63	(10.00)
Female	11.66 ±	6.77	(10.00)
Total	11.11 ±	6.31	(10.00)

High value of standard deviation indicates the inhomogeneity of this parameter in the examined sample, which is supported by the fact that the minimum of DM duration is one, and the maximum is 38 years. Female subjects have longer DM duration, but not statistically significantly longer vs. male subjects.

Glycosylated hemoglobin (HbA1c) values at the time of transition to insulin therapy were 10.51%, which is statistically significantly higher than 6 months before conversion to insulin (0.88%) (Table 3).

Kohen's d indicates the average effect of drug therapy in the period of 6 months before insulin initiation (Table 4).

Fasting glycemia also increased at the time of insulin initiation vs. 6 months before.

Table 3. HbA1c % at insulin therapy initiation and 6 months before

HbA1c %					
Insulin therapy initiation			6 months before insulin therapy initiation		
10.51 ±	1.49	(10.50)	9.63 ±	1.18	*** (9.65)
Δ (Pr. – 6 months before)			Δ (Pr. – 6 months after)		
0.88 ±	1.16	(0.85)	2.24 ±	1.10	(2.00)

*** - p < 0.001

Table 4. Fasting glycemia (mmol/l) at the time of insulin initiation, and 6 months before insulin initiation

Fasting glycemia (mmol/l)					
Insulin initiation			6 months before		
12.40 ±	2.86	(12,15)	11.81 ±	2.61	(11.50)
Δ (Pr. – 6 months before)			Δ (Pr. – 6 months after)		
0.59 ±	3.39	(0.75)	3.84 ±	2.88	(3.45)

*** - p < 0.001

Discussion

The study included 70 patients - 41 women (59%) and 29 men (41%). The mean age of the patients was 60.97 years. This finding was comparable to similar studies.

Duration of diabetes in our patients was 11.11 years, which is more than in patients in Germany's study INSTIGATE (19), where the insulin therapy is initiated much earlier.

The data about average diabetes duration might be considered with caution since establishing diagnosis of diabetes is often significantly delayed in real life. Evidences of elderly patients with a short known duration of diabetes, duration of around one year, but with marked hyperglycemia and already present complications of diabetes are supporting this claim (20).

Data about glycaemic control and especially in relation to HbA1c, are the most significant finding in the study and they are showing that insulin therapy is initiated with an average hemoglobin of 10.51%. This value of HbA1c is significantly higher than in all comparable studies conducted in Europe and America (19, 21-25). In a similar study (INSTIGATE) (19) in Germany and Spain, insulin therapy was initiated at HbA1c 9.2% and in Greece 9.7%. In the BiAsp/Glargine (21) study conducted in the USA, at the time of insulin administration HbA1c was 9.0%, while in the BIAsp-1556 study in Serbia HbA1c was 10.68%. The BIAsp study was conducted in Serbia and was among the first studies to indicate the late initiation of insulin therapy. (26, 27).

Compared to the period of 6 months before initiation of insulin therapy, there was a significant increase in HbA1c by 0.88%, which unequivocally showed that all patients could be introduced with insulin therapy even 6 months earlier, due to the fact that HbA1c was 9.63 ± 1.18% at that time. Even UKPDS (8, 9) study have shown that decrease in HbA1c values by only 1% leads to a reduced risk of microvascular complications by 33% (5-7). Delay of insulin therapy initiation did not bring any benefit to patients, but on the contrary an increase in HbA1c, which, according to available knowledge, increases the risk of late complications of diabetes (28).

Conclusion

In patients with type 2 diabetes on (sub) maximal therapy with oral hypoglycemics that have been poorly regulated for a long period of time, the initiation of insulin therapy is often delayed. Insulin therapy was initiated to patients in our research at HbA1c of 10.51%, which is significantly higher than in comparable studies in Europe and USA. This delay might be considered to be at least 6 months since the tests performed at that time (HbA1c - 9.63%) are suggesting that even then all the criteria for insulin therapy initiation were present.

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DA LI SE KASNI SA UVOĐENJEM INSULINSKE TERAPIJE KOD BOLESNIKA SA DIJABETESOM TIP 2 U KLINIČKOJ PRAKSI?

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U svakodnevnoj kliničkoj praksi, veliki broj bolesnika sa dijabetesom tip 2 (T2D) je loše regulisan, što doprinosi nastanku hroničnih komplikacija dijabetesa. Kasno otpočinjanje insulinske terapije u T2D predstavlja posebno značajan uzrok dugotrajno loše glikoregulacije. Postoje različiti uzroci ovog kašnjenja, ali u Srbiji, kao i u Nišu, kao centru juga Srbije, nema dovoljno raspoloživih podataka. Da bi utvrdili da li kašnjenja u otpočinjanu insulinske terapije ima u Nišu, koliko je kašnjenje u odnosu na preporuke i iskustva drugih, kakva je glikoregulacija bila šest meseci pre otpočinjanja insulinske terapije i da li je tada trebalo otpočeti insulinsku terapiju, sproveli smo navedeno ispitivanje.

Prema sprovedenom ispitivanju, u vreme otpočinjanja insulinske terapije HbA1c bio je 10,51%, što je značajno više u odnosu na druge komaparabilne studije. Može se smatrati da je kašnjenje najmanje 6 meseci, jer je tada HbA1c bio 9,63% i bili su ispunjeni svi kriterijumi za otpočinjanje insulinske terapije.

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Ključne reči: *dijabetes mellitus tip 2, otpočinjanje insulinske terapije, HbA1c, odlaganje*