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Improvement of blood glucose control and reduction of hypoglycemia, body weight, and C-reactive protein in type 1 diabetic patients treated with intensive insulin therapy with insulin analogs

Poboljšanje glikoregulacije, snižavanje broja hipoglikemija, telesne mase i nivoa C-reaktivnog proteina kod bolesnika sa dijabetesom melitusom tipa 1 na intenziviranoj insulinskoj terapiji analozima insulina

Saša Radenković, Milena Velojić Golubović, Dragan Dimić, Danijela Radojković, Vojislav Ćirić, Milica Pešić

University Clinical Center Niš, Clinic for Endocrinology, Diabetes and Metabolic Diseases, Niš, Serbia; University of Niš, Faculty of Medicine, Niš, Serbia

Abstract

Background/Aim. Good metabolic control can delay the onset and progression of chronic complications of diabetes mellitus (DM). Intensified insulin therapy (IIT) is the cornerstone of good metabolic control in the treatment of type 1 DM (T1DM) while avoiding hypoglycemia and body weight (BW) gain in those patients. The aim of the study was to assess the effects of IIT with insulin analogs (aspart and glargine) in T1DM patients. **Methods.** This prospective clinical study included 49 patients with at least one year of T1DM duration, who were on IIT with human insulin at that moment. They commenced therapy with insulin aspart for three months, followed by insulin glargine for another three months. An analysis of blood glucose (BG) control (glycated hemoglobin – HbA1c, mean BG, fasting BG, postprandial BG, and glycemic variability) and analysis of BW, hypoglycemia, and C-reactive protein (CRP) levels were performed. **Results.** The HbA1c level decreased slightly (non-significantly) after three months of insulin aspart therapy (from 9.28% to 8.83%) and decreased significantly after the aspart/glargine combination (to 8.08%; $p < 0.001$). After the first three months with aspart therapy, a significant reduction in postprandial BG was noted after all three main meals. The mean postprandial rise of BG was significantly reduced. The variability of daily BG was significantly reduced (standard deviation of BG fell from 2.28 mmol/L to 1.90 mmol/L; $p < 0.05$). The mean BG value in the profiles decreased (from 9.11 mmol/L to 8.31 mmol/L; $p < 0.05$). All BG values in the profiles after six months were statistically significantly lower compared to the initial values, as well as the mean BG (6.88 mmol/L; $p < 0.001$) and the variability of daily BG (1.49 mmol/L; $p < 0.01$). Our results showed a significant reduction in the number of hypoglycemias after three months, especially after the introduction of insulin glargine therapy (significant reduction in the number of symptomatic, asymptomatic, and nocturnal hypoglycemias). The results showed a discrete but significant reduction in BW and a significant reduction in CRP levels (from 3.43 mg/L to 2.25 mg/L; $p < 0.001$). **Conclusion.** Treatment of patients with T1DM with insulin analogs (insulin aspart and insulin glargine) in IIT leads to improved BG control with a reduction in the number of hypoglycemia, BW, and CRP levels.

Key words:
c-reactive protein; diabetes mellitus, type 1; glycated hemoglobin; glycemic control; hypoglycemia; insulin, long-acting; insulin, short-acting.

Apstrakt

Uvod/Cilj. Dobra metabolička kontrola može odložiti nastanak i napredovanje hroničnih komplikacija dijabetesa melitusa (DM). Intenzivirana insulinska terapija (IIT) je kamen temeljac dobre metaboličke kontrole u lečenju bolesnika sa tipom 1 DM (T1DM), uz izbegavanje hipoglikemije i povećanja telesne mase (TM) kod tih bolesnika. Cilj rada bio je da se procene efekti primene IIT analozima insulina (aspart i glargin) na obolele od T1DM. **Metode.** Prospektivnim kliničkim istraživanjem obuhvaćeno je 49 bolesnika sa T1DM u trajanju od najkraće jedne godine, koji su tada bili na IIT humanim insulinima. Uveden im je insulin aspart u trajanju od tri meseca, a zatim insulin glargin takođe u trajanju od tri meseca. Urađena im je analiza nivoa glukoze u krvi (GK) (glikoziliranog hemoglobina – HbA1c, srednjeg nivoa GK, GK natašte, postprandijalne GK i glikemijske varijabilnosti) i analiza

Correspondence to: Saša Radenković, University Clinical Center Niš, Clinic for Endocrinology, Diabetes and Metabolic Diseases, Bulevar Dr. Zorana Djindjića 48, 18 000 Niš, Serbia. E-mail: doktor.sasa@gmail.com; rale@ni.ac.rs

TM, broja hipoglikemija i nivoa C-reaktivnog proteina (CRP). **Rezultati.** Nivo HbA1c je posle tri meseca terapije insulinom aspart bio neznatno (bez značajnosti) snižen (sa 9,28% na 8,83%), a posle kombinacije aspart/glargin bio je značajno snižen (na 8,08%; $p < 0,001$). Posle prva tri meseca, zabeleženo je značajno ublažavanje nivoa postprandijalne GK nakon sva tri glavna obroka. Srednji postprandijalni porast GK bio je značajno smanjen. Varijabilnost dnevne GK je bila značajno smanjena (standardna devijacija dnevne GK smanjena je sa 2,28 mmol/L na 1,90 mmol/L; $p < 0,05$). Srednja vrednost GK u profilima je opala (sa 9,11 mmol/L na 8,31 mmol/L; $p < 0,05$). Sve vrednosti GK u profilima posle šest meseci bile su statistički značajno niže u odnosu na početne vrednosti, kao i srednje vrednosti GK (6,88 mmol/L; $p < 0,001$) i varijabilnost dnevne GK (1,49 mmol/L; $p < 0,01$). Naši rezultati pokazali su značajno smanjenje broja hipoglikemija posle tri meseca, a posebno nakon uvođenja terapije insulinskim analogom glargin (značajno smanjenje broja simptomatskih, asimptomatskih i noćnih hipoglikemija). Rezultati su pokazali diskretno, ali značajno smanjenje TM i značajno sniženje nivoa CRP (sa 3,43 mg/L na 2,25 mg/L; $p < 0,001$). **Zaključak.** Terapija obolelih od T1DM analozima insulina (insulin aspart i insulin glargin) u IIT dovodi do poboljšanja kontrole GK sa smanjenjem broja hipoglikemija, TM i nivoa CRP.

Ključne reči:
c-reaktivni protein; dijabetes melitus, tip 1; hemoglobin a, glukozilovan; glukoza u krvi, kontrola; hipoglikemija; insulin, dugodelujući; insulin, kratkodelujući.

Introduction

Intensified insulin therapy (IIT) is the cornerstone of good glycemic control and provides a reduction of risk for developing chronic vascular complications of type 1 diabetes mellitus (DM) – T1DM, as documented in the Diabetes Control and Complications Trial (DCCT) [1].

The beginning of the 21st century in modern diabetology is the decade of insulin analogs. By minor changes in the sequence of amino acids in the peptide chains of insulin, an attempt is made to ensure a change in pharmacokinetics, thus providing better control of glycemia both during and after meals [2, 3]. IIT has two permanent goals: to achieve as good blood glucose (BG) control as possible while reducing the frequency and severity of hypoglycemia.

Although many metabolic abnormalities contribute to the overall risk of developing chronic diabetic complications, hyperglycemia remains the hallmark of DM [4]. Glycated hemoglobin (HbA1c) provides an integrated measure of glucose exposure during the day, where its absolute level is contributed by the level of both fasting BG (FBG) and postprandial glycemia (PPG) [5–8]. PPG contributes significantly to the mean glycemic value, which is a key indicator of glycemic control measured through the HbA1c level. Such findings represent the basis for the formation of the glucose triad model in the treatment of DM. Treatment goals are represented with three glycemic parameters: HbA1c, PPG, and FBG. They are related to each other and represent necessary goals for therapy that try to optimize glycemic control [9].

One of the possibilities is that the risk of complications depends on the magnitude of postprandial spikes in glycemia and the effect of counterregulatory hormones released in hypoglycemia. This is how we came to the concept of variability of daily glycemia and the discussion about its importance [10, 11].

The aim of this study was to assess the effectiveness of IIT with analogs of human insulin through the analysis of glycemic control parameters (levels of HbA1c, FBG, PPG, the mean level of BG, and glycemic variability) and to test the safety of IIT with analogs of human insulin through analysis of the number and severity of hypoglycemia and analysis of changes in body weight (BW).

Methods

This prospective study included patients with T1DM from the University Clinical Center Niš, Serbia, Faculty of Medicine, Clinic for Endocrinology, Diabetes, and Metabolic Diseases. The study was approved by the Institutional Ethical Committee (No. 10413/17), and written consent was obtained from all subjects. Data analysis was performed on 49 patients with a clear diagnosis of T1DM and at least one year of duration of the disease and insulin therapy and who were currently on IIT with human insulins. They were first examined on the existing therapy in a monthly period with the aim of achieving the target glycemic control by correcting the therapy. During that period, patients had weekly check-ups. In addition to regular daily self-monitoring of BG, patients performed glycemic profiles regularly once a week by self-monitoring of BG immediately before and two hours after the main meals (six measurements in total) with measurements before bedtime and at night (at 3 a.m.). The patients were re-educated about the dietary regime, the importance of self-monitoring of BG and the method of correcting the bolus dose, about hypoglycemia, and the way of recording them. Patients had the possibility of 24-hour telephone contact, 7 days a week, with a doctor, a nurse educator, and members of the team who followed them. During the last week of that period, patients performed two daily glycemic profiles.

After that, patients started therapy with a fast-acting analog of human insulin, insulin aspart, instead of human soluble insulin. On the day of the introduction into the therapy of a fast-acting analog of human insulin, the patients underwent a detailed anamnestic, clinical, and biochemical examination (visit 1 – V1). In the following period of three months, regular controls continued, which included correction of insulin therapy according to the results of self-monitoring of BG and control at the Clinic once a month. In

the last week of this period, patients performed two all-day glycemic profiles.

Then, patients started therapy with a long-acting insulin analog, insulin glargine, instead of intermediate-acting human insulin. On the day of the introduction of long-acting human insulin analog therapy, the patients underwent a detailed examination (visit 2 – V2). In the following period of three months, regular controls continued, which included correction of insulin therapy according to the results of self-monitoring of BG and control at the Clinic once a month. In the last week of this period, patients performed two all-day glycemic profiles. At the end of this period, the patients underwent a detailed examination (visit 3 – V3).

The insulin dose was corrected (both basal and boluses) in order to achieve fasting BG levels of 4 to 6 mmol/L and preprandial levels of 5 to 7 mmol/L, i.e., postprandial levels of 5 to 10 mmol/L, bedtime levels of 6 to 8 mmol/L, and at night from 5 to 8 mmol/L. Doses of prandial boluses (both human insulin and insulin aspart) were adjusted depending on BG and according to the level of education of the patients, the size of the meal, and the level of physical activity.

Detailed anamnestic and clinical workup at each check-up included the following: recording anamnestic data on the duration of DM, previous therapy, complications, complaints, and the number and degree of severity of hypoglycemia in the period before control; taking anthropometric measurements [BW and body height (BH) from which the body mass index (BMI) is calculated]. BW was measured in a standing position, using a decimal scale, in patients with light clothing and without shoes and rounded to the nearest 100 g. BH was measured by a standard height meter in a standing position without shoes, with a normal shoulder position. BMI was determined by dividing the BW in kg by the square of BH in m (kg/m^2).

The American Diabetes Association (ADA) Workgroup proposed the following classification of hypoglycemia in diabetes: mild and severe, symptomatic and asymptomatic, and nocturnal hypoglycemia [12].

Hypoglycemias were recorded and collected from patient diaries. Mild hypoglycemia was defined as symptoms indicating hypoglycemia that resolved after taking a meal, with measured glycemic values less than 3.9 mmol/L, which patients could manage on their own, without the help of other people. Asymptomatic hypoglycemias are all measured glycemic values less than 3.9 mmol/L during regular self-monitoring, which are not accompanied by characteristic symptoms. Severe hypoglycemias were defined as hypoglycemias in which the patient had symptoms of hypoglycemia that required the assistance of another person (either a family member or medical staff) and recovery after administration of oral or intravenous (i.v.) glucose or glucagon. Nocturnal hypoglycemias were defined as all hypoglycemias occurring between bedtime and morning (from around 11 p.m. to 7 a.m.).

Biochemical measurements were done in all patients at the beginning of the study (before the introduction of therapy with a fast-acting insulin analog), after three months, and after six months (V1, V2 and V3).

Blood samples were taken in the morning after a twelve-hour overnight fasting from the antecubital vein of patients in a sitting position. Blood centrifugation was performed 30 to 45 min after collection. Biochemical analyses were performed at the University Clinical Center Niš, Center for Medical Biochemistry on the day of blood collection.

Assessment of glycoregulation was performed by analyzing the HbA1c level and analyzing the glycemic profile at 8 points (BG before the main meals and two hours after the main meals, before going to bed, and at 3 a.m.). HbA1c was determined by the immunochemical method with Olympus reagents on the Olympus AU 680 automatic analyzer [reference range (RR) 4.2–6.2%]. The patients performed glycemic profiles regularly by self-monitoring of BG using a calibrated memory glucose meter (RR 3.9–6.1 mmol/L). Preprandial BG, PPG, nighttime BG value (at 3 a.m.), mean daily BG value, and variability of mean daily BG were analyzed separately.

Hematological parameters were determined on a hematological analyzer AL 816 (Graz, Austria) [RR for erythrocytes (Er) 3.8–6.0 $\times 10^{12}$/L; leukocytes (Le) 4.0–10.0 $\times 10^{9}$/L; thrombocytes (Tr) 150–450 $\times 10^{9}$/L; hemoglobin (Hb) 110–170 g/L], while Er sedimentation rate (ESR) was done in vacuum test tubes from Terumo (Leuven, Belgium) according to the modified Westergreen method (RR < 12 mm/h). Determination of C-reactive protein (CRP) was done by immunoturbidimetric method on multi-channel analyzer Olympus AU 400, expressed in mg/L (RR 0.0–5.0 mg/L), and fibrinogen – by the immunoturbidimetric method using saturated Parfontier solution, on the Beckman DU 650 apparatus, expressed in g/L (RR 2.0–4.0 g/L).

Statistical analysis

Data entry, tabular and graphical presentation were performed using MS Office Excel, and statistical calculations were performed using SPSS, version 22.0. Attributive parameters are represented by frequencies and percentages, and continuous (measurable) parameters are represented by means and standard deviations (SD) and median (Md). The normality of the distribution of parameters was determined by the Shapiro-Wilk test. Student's *t*-test of dependent (paired) samples (for normal distributions) and Wilcoxon Signed Ranks Test (for distributions deviating from normal) were used to test the statistical significance of the difference in the values of continuous parameters between visits. The value of p less than 0.05 was considered statistically significant.

Results

The prospective study included 49 subjects with T1DM, of which 27 (55.10%) were male; average age was 29.94 ± 4.98 years, with a median of 29 years; average duration of T1DM was 13.94 ± 7.70 years, with a median of 13 years; average BH was 172.51 ± 7.21 cm, with a median of 171 cm.

The results of monitoring glycoregulation parameters, HbA1c and BG values in daily profiles, the mean value of daily BG, and variability of daily BG level of SD and coefficient of variation (CV) of BG in daily profiles, are shown in Table 1.

The HbA1c level shows a decrease after the third month of therapy [non-significant (ns)], and it is significantly lower after the sixth month of therapy ($p < 0.001$), compared to the beginning of therapy and to V2 ($p < 0.01$) (Wilcoxon test).

The mean value of BG in the profile was statistically significantly higher at V1 than at V2 ($p < 0.05$) (Student's *t*-test) and also at V3 ($p < 0.001$) (Wilcoxon test). The value was higher at V2 than at V3 ($p < 0.001$) (Wilcoxon test).

Changes in the level of HbA1c and the mean value of daily BG in the daily profiles are shown in Figure 1.

The level of FBG did not change significantly after the third month of therapy compared to the level at the beginning of therapy, but it was statistically significantly lower after the sixth month of therapy compared to the level at V1 and also at V2 ($p < 0.001$) (Wilcoxon test).

All other values of BG measured in the mentioned periods, as well as mean values of BG in the profile, SD of MBG in the profile, and CV of MBG in the profile, were the highest at the beginning of therapy. The values were lower after the third month of therapy, and the lowest after the sixth month of therapy. Relationships and differences in BG levels in the profiles are shown in Figures 2 and 3.

Table 1

Blood glucose values in daily profiles and glycated hemoglobin before and after insulin analog therapy

Parameter	V1		V2		V3	
	mean ± SD	median	mean ± SD	median	mean ± SD	median
Breakfast						
before	8.14 ± 2.91	^{g***} 7.90	8.68 ± 3.07	^{g***} 8.30	6.19 ± 1.84	5.60
after	10.42 ± 2.78	^{a**g***} 10.60	9.01 ± 2.25	^{g***} 8.90	7.41 ± 1.73	7.30
Lunch						
before	8.32 ± 2.43	^{g**} 8.70	7.75 ± 2.51	^{g*} 7.80	6.77 ± 1.98	6.60
after	10.84 ± 4.45	^{a**g***} 10.40	8.64 ± 2.95	^{g**} 8.60	6.96 ± 1.92	6.70
Dinner						
before	8.09 ± 2.91	^{g***} 7.80	7.89 ± 2.40	^{g***} 7.60	6.33 ± 1.58	6.30
after	9.80 ± 3.36	^{a*g***} 9.10	8.27 ± 2.99	7.40	7.22 ± 2.38	6.90
Before bed	9.03 ± 2.33	^{g***} 8.50	8.34 ± 2.53	^{g**} 8.10	7.01 ± 1.87	6.70
Night (03 a.m.)	8.23 ± 2.40	^{g*} 8.40	7.88 ± 2.50	7.50	7.16 ± 1.95	6.50
MBG	9.11 ± 2.24	^{a*g***} 9.23	8.31 ± 1.86	^{g***} 8.30	6.88 ± 1.27	6.61
SD of BG	2.28 ± 0.78	^{a*g***} 2.30	1.90 ± 0.84	^{g**} 1.85	1.49 ± 0.52	1.50
CV of BG	25.30 ± 7.73	^{g*} 23.48	23.17 ± 9.68	21.22	21.74 ± 6.50	20.78
HbA1c	9.28 ± 1.50	^{g***} 9.20	8.83 ± 1.61	^{g**} 8.50	8.08 ± 1.46	7.80

V1 – visit 1; V2 – visit 2; V3 – visit 3; BG – blood glucose (mmol/L); MBG – mean BG; SD – standard deviation; CV – coefficient of variation; HbA1c – glycated hemoglobin (%).
Statistical significance: a – vs. V2; g – vs. V3; * $p < 0.05$ (Student's *t*-test); ** $p < 0.01$; *** $p < 0.001$ (Wilcoxon test).

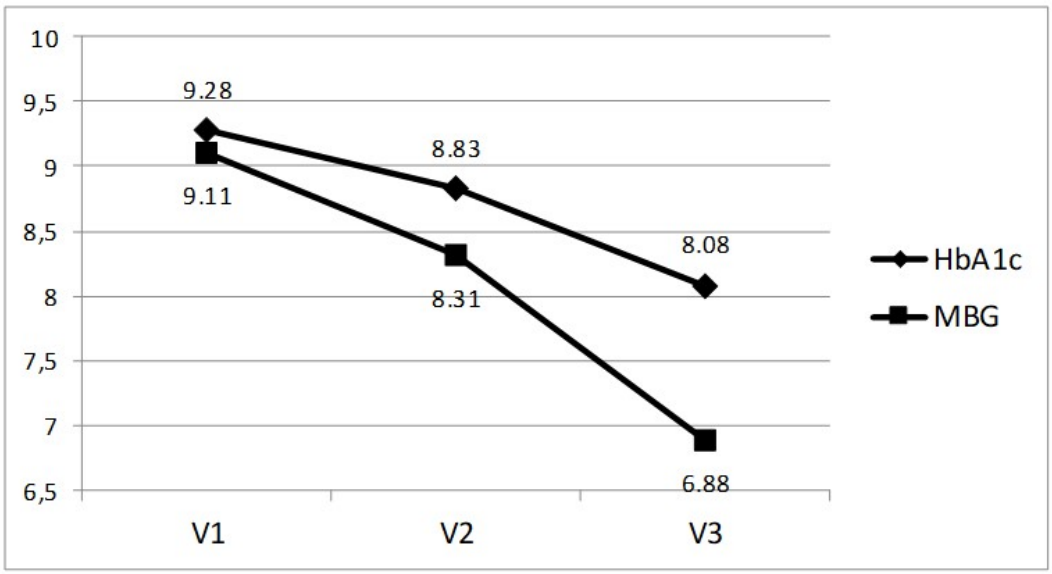

Fig. 1 – The change in the level of glycated hemoglobin (HbA1c) (%) (p = ns, V1 vs. V2; $p < 0.01$, V2 vs. V3; $p < 0.001$, V1 vs. V3) and mean blood glucose – MBG (mmol/L) ($p < 0.05$, V1 vs. V2; $p < 0.001$, V2 vs. V3; $p < 0.001$, V1 vs. V3) during therapy. ns – non significant. For other abbreviations, see Table 1.

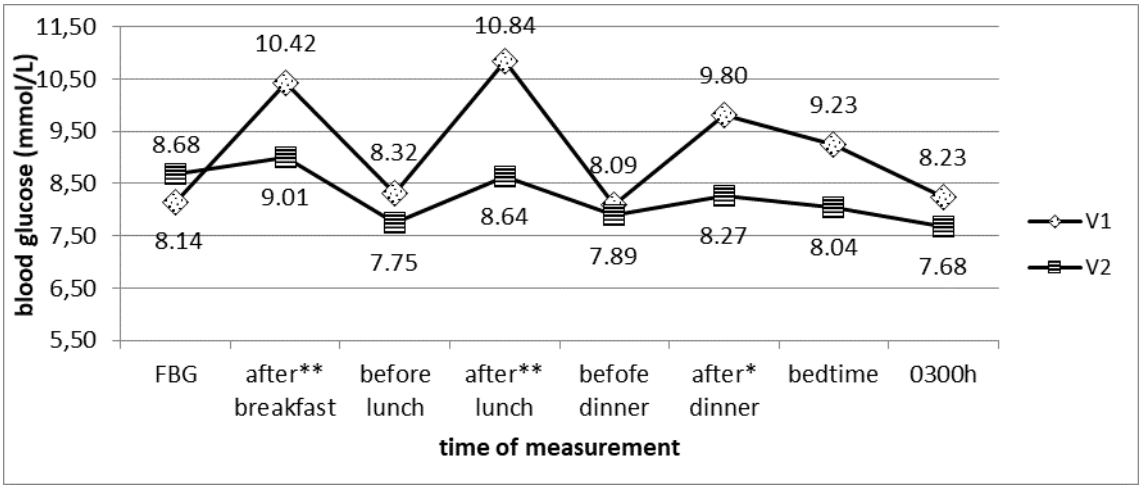

Fig. 2 – The mean of two eight-point blood glucose (BG) profiles at the beginning of therapy (V1) and after insulin aspart therapy, i.e., after the first three months (V2).
FBG – fasting BG; * $p < 0.05$; ** $p < 0.01$.

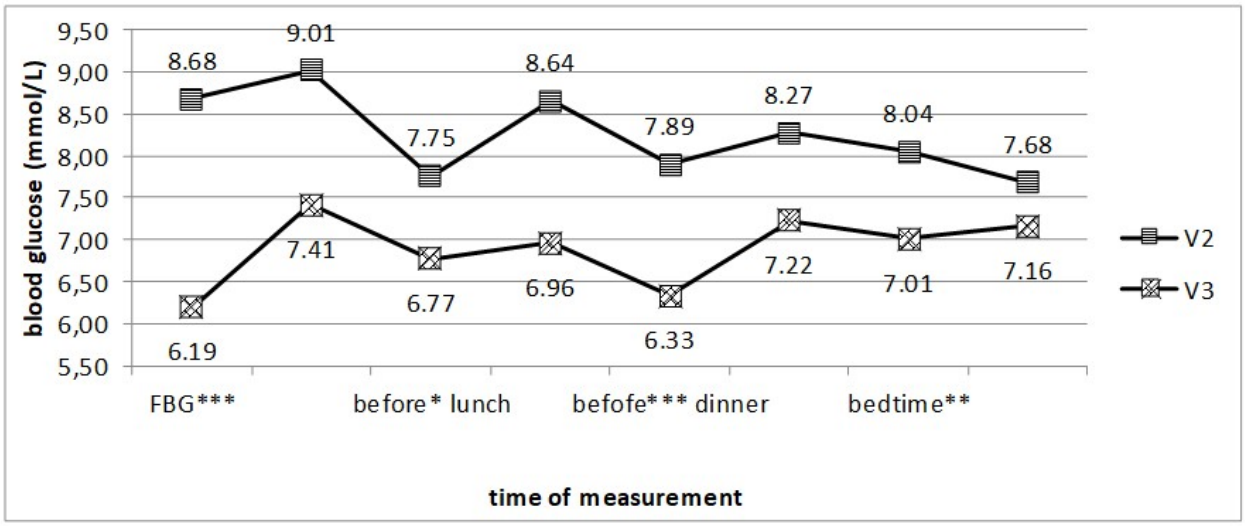

Fig. 3 – The mean of two eight-point blood glucose (BG) profiles after therapy with insulin aspart, i.e., after the first three months (V2) and after therapy with insulin aspart/glargine, i.e., after six months (V3).
FBG – fasting BG; * p < 0.05; ** p < 0.01; *** p < 0.001.

The levels of BG after breakfast, before and after lunch, before and after dinner, and at bedtime were almost all statistically significantly higher at the beginning of therapy compared to values after the third month of therapy as well as after the sixth month of therapy.

The level of BG during the night showed a slight decrease during the study and was statistically significantly lower after the sixth month of therapy than at the beginning ($p < 0.05$) (Wilcoxon test).

The values of the SD of BG in the profile were statistically significantly higher at V1 than at V2 ($p < 0.05$) (Student's *t*-test) and also at V3 ($p < 0.001$) (Wilcoxon test). The values were higher at V2 than at V3 ($p < 0.01$) (Wilcoxon test). The value of CV of BG in the profile was higher at the beginning of therapy than after the sixth month of therapy ($p < 0.05$) (Wilcoxon test).

In order to evaluate the effect of therapy on reducing the prandial increase (PI) in BG after all three meals individually and the total average PI in BG during the day, the mean PI in BG (BG after a meal – BG before a meal) was determined for all three main meals and the mean PI during the day. The results are shown in Table 2 and Figure 4.

The value of the PI in BG for dinner was higher at the beginning of therapy than after the third month ($p < 0.05$) (Student's *t*-test). The value of the PI in BG was at the same level of statistical significance for lunch, while higher levels of statistical significance were present for breakfast ($p < 0.01$) and the mean PI in BG ($p < 0.001$) (Wilcoxon test).

The value of the PI in BG for breakfast at the beginning of therapy was higher than after six months of therapy ($p < 0.05$) (Wilcoxon test); the values of the PI in BG for lunch and the mean PI in BG were statistically significantly higher at the beginning of therapy than after six months of therapy ($p < 0.001$) (Student's *t*-test).

The number of hypoglycemic episodes (number of hypoglycemia *per* patient *per* month) decreased during the

Table 2

Values of prandial increase in blood glucose (mmol/L) before and after insulin analog therapy

Prandial increase	V1		V2		V3	
	mean ± SD	median	mean ± SD	median	mean ± SD	median
Breakfast	2.28 ± 2.36	a**g* 2.40	0.33 ± 2.86	0.90	1.22 ± 2.07	1.30
Lunch	2.52 ± 3.44	a* g*** 3.10	0.89 ± 2.52	0.80	0.20 ± 1.94	0.60
Dinner	1.72 ± 3.24	a* 2.00	0.38 ± 2.42	0.60	0.89 ± 1.79	0.90
Mean	2.17 ± 1.74	ag*** 2.30	0.54 ± 1.67	0.73	0.77 ± 1.19	0.83

V1 – visit 1; V2 – visit 2; V3 – visit 3; SD – standard deviation.
Statistical significance: a – vs. V2; g – vs. V3; * $p < 0.05$ (Student's *t*-test); ** $p < 0.01$; *** $p < 0.001$ (Wilcoxon test).

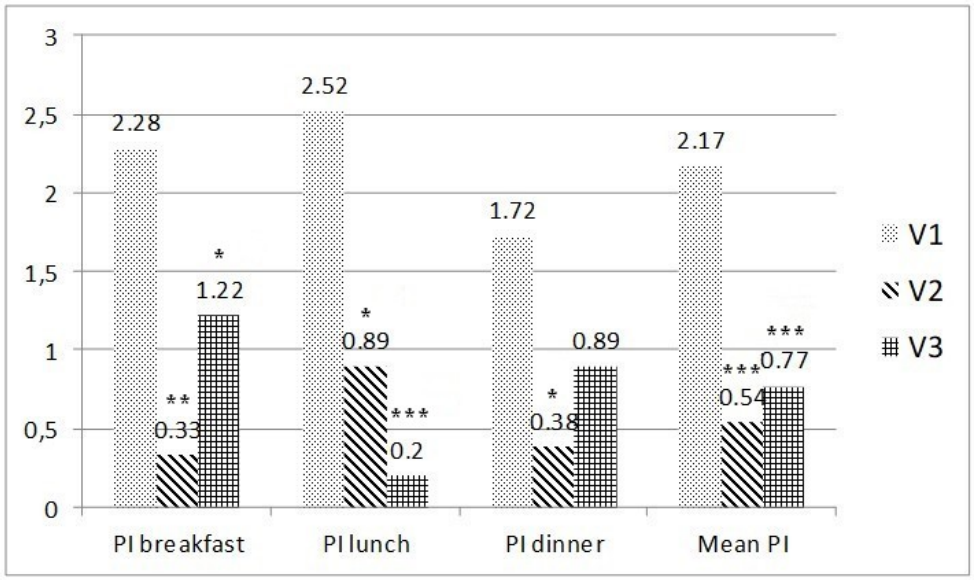

Fig. 4 – The change in the level of prandial increase (PI) in blood glucose (mmol/L) after all three meals individually and the total mean PI in blood glucose during the day (*$p < 0.05$ vs. V1; **$p < 0.01$ vs. V1; ***$p < 0.001$ vs. V1).
V2, V2, and V3 – visits, respectively. For an explanation, see Figures 2 and 3.

Table 3

Hypoglycemic episodes *per* patient *per* month before and after insulin analog therapy

Hypoglycemic episodes	V1		V2		V3	
	mean ± SD	median	mean ± SD	median	mean ± SD	median
Symptomatic	8.59 ± 6.32	a*g*** 10	6.10 ± 4.66	g*** 6	4.53 ± 3.60	4
Asymptomatic	5.96 ± 5.09	g** 6	4.96 ± 4.28	g*** 5	2.76 ± 3.25	1
Severe	0.08 ± 0.28	0	0.04 ± 0.20	0	0.02 ± 0.14	0
All	14.63 ± 9.77	g*** 16	11.10 ± 7.53	g*** 12	7.31 ± 5.09	8
Nocturnal	3.98 ± 3.91	g*** 4	3.14 ± 2.90	g*** 3	1.76 ± 1.75	2

V1 – visit 1; V2 – visit 2; V3 – visit 3; SD – standard deviation.
Statistical significance: a – vs. V2; g – vs. V3; * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$ (Wilcoxon test).

course of therapy. Episodes of serious hypoglycemia whose number was too small for statistical analysis were excluded from the analysis. During one month of therapy with only human insulin, there were four severe hypoglycemias. During the first three months of therapy, there was a total of six severe hypoglycemias, i.e., two *per* month. During the last three months of therapy, a total of three hypoglycemias occurred, i.e., only one *per* month. Their number also evidently decreased during the study.

The total number of hypoglycemic episodes *per* patient *per* month was statistically significantly lower at V3 compared to the number of these episodes at V2, as well as compared to V1 ($p < 0.001$) (Wilcoxon test). The number of asymptomatic hypoglycemic episodes *per* patient *per* month was lower when comparing the V1 and V3 ($p < 0.01$) (Table 3). The lower number of symptomatic hypoglycemic episodes *per* patient *per* month was during the first three months of therapy compared to the period of human insulin therapy ($p < 0.05$). The number of nocturnal hypoglycemias did not statistically change after the first three months, but at V3, it was statistically significantly lower ($p < 0.001$) compared to V2 and V1.

Differences in insulin dose level and BW, i.e., BMI, are shown in Table 4 (compared by Student's *t*-test).

The total daily dose of insulin at the beginning of therapy was statistically significantly higher than after the sixth month of therapy ($p < 0.001$). Furthermore, the total daily dose of insulin at V2 was statistically significantly higher than at V3 ($p < 0.01$).

The total bolus dose at the beginning of therapy (dose of human regular insulin) was statistically significantly higher than the dose of insulin aspart at V2 and V3 ($p < 0.001$); also, the dose of insulin aspart at V2 was higher than at V3 ($p < 0.001$).

The total dose of basal insulin at the end of the third month of therapy and after the sixth month of therapy is statistically significantly higher compared to the dose of basal insulin at the beginning of therapy ($p < 0.001$).

The total daily dose of insulin expressed in unit (U) *per* kg of BW was the highest at the beginning of therapy, higher than at V3 ($p < 0.01$). The total daily dose of insulin at V2 was higher than at V3 ($p < 0.05$).

The values of BW and BMI were higher at the beginning of therapy ($p < 0.05$) and also after the third month of therapy ($p < 0.01$) compared to the values after the sixth month of therapy.

The values of all tested hematological parameters (complete blood count) did not differ statistically significantly during the test period (Table 5). There was no statistically significant difference between ESR values before and after insulin analog therapy in the study period. There was a statistically significant drop in the level of CRP, i.e., the level of CRP at the beginning of therapy was statistically significantly higher than after the third or sixth month of therapy at the level of maximum statistical significance of $p < 0.001$, while the level of fibrinogen was statistically significantly higher after the sixth month of therapy compared to the beginning of therapy ($p < 0.01$) (Wilcoxon test).

Discussion

T1DM is treated from the very beginning with insulin therapy. Over the years, insulin therapy has been improved by the discovery of new techniques for obtaining more and more purified preparations, as well as ways to change the pharmacokinetics of certain insulin preparations to provide daily therapy that would correspond as closely as possible to the physiological profile of insulin secreted by a healthy pancreas [13].

The leading type of modern insulin therapy for T1DM, and proposed by practically all recommendations, is the so-called IIT, or basal-bolus therapy, or multiple daily insulin injections. It involves providing basal insulinization with one or two injections of intermediate-acting human insulin (Neutral Protamine Hagedorn – NPH insulin) with the administration of three or more boluses of human soluble insulin (regular insulin) before the main meals [14–16]. The profile of the action of the human insulin preparation could not fully provide an insulin profile identical to the physiological one. In short, rapid- and short-acting human insulin has an effect that is neither fast enough nor short enough. Intermediate-acting insulin preparations (NPH or lente insulins) do not have an effect that is long enough and, more importantly, that is sufficiently uniform over 24 hrs [17–19].

Table 4

The levels of daily dose of insulin, body weight and body mass index before and after insulin analog therapy

Parameter	V1		V2		V3	
	mean ± SD	median	mean ± SD	median	mean ± SD	median
Bolus dose	34.29 ± 8.45	^{ag***} 36.00	31.55 ± 7.86	^{g***} 30.00	29.22 ± 7.77	30.00
Basal dose	25.59 ± 5.35	^{ag***} 26.00	27.18 ± 5.98	26.00	27.63 ± 6.28	28.00
TDD (U)	59.88 ± 12.79	^{g***}60.00	58.73 ± 13.02	^{g**} 60.00	56.86 ± 13.43	58.00
TDD (U/kg BW)	0.86 ± 0.18	^{g**} 0.88	0.84 ± 0.19	^{g*} 0.83	0.82 ± 0.19	0.80
BW (kg)	70.43 ± 10.84	^{g*} 70.00	70.49 ± 11.01	^{g**} 70.00	69.96 ± 11.20	70.00
BMI (kg/m²)	23.59 ± 2.81	^{g*} 23.95	23.61 ± 2.85	^{g**} 24.06	23.42 ± 2.88	23.71

TDD – total daily dose of insulin; BW – body weight; BMI – body mass index.
Statistical significance: a – vs. 2; g – vs. 3; * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$ (Student's *t*-test).

Table 5

Values of parameters of inflammation and complete blood count before and after insulin analog therapy

Parameter	V1		V2		V3	
	mean ± SD	median	mean ± SD	median	mean ± SD	median
CRP (mg/L)	3.43 ± 2.03	^{ag***} 3.20	2.25 ± 1.39	2.10	2.07 ± 1.62	1.40
Fibrinogen (g/L)	3.33 ± 0.87	^{g**} 3.20	3.60 ± 1.04	3.50	3.87 ± 1.18	3.80
ESR (mm/h)	14.69 ± 13.04	12.00	13.47 ± 11.77	10.00	16.29 ± 14.55	14.00
Le ($\times 10^9$/L)	7.42 ± 1.81	7.30	6.98 ± 1.84	7.00	6.89 ± 1.93	6.70
Er ($\times 10^{12}$/L)	4.82 ± 0.42	4.84	4.84 ± 0.48	4.88	4.82 ± 0.45	4.85
Hb (g/L)	152.06 ± 11.20	152.00	150.63 ± 12.87	151.00	150.49 ± 12.03	148.00
Tr ($\times 10^9$/L)	256.84 ± 60.43	257.00	246.86 ± 65.66	242.00	264.00 ± 60.81	256.00

V1 – visit 1; V2 – visit 2; V3 – visit 3; SD – standard deviation; CRP – C-reactive protein; ESR – erythrocyte sedimentation rate; Le – leucocytes; Er – erythrocytes; Hb – hemoglobin; Tr – thrombocytes.
Statistical significance: a – vs. V2; g – vs. V3; *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$ (Wilcoxon test).

Modified insulins (insulin analogs), with their superior pharmacokinetic profile, can provide easier overcoming of the problem of strict metabolic control, i.e., provide better control of glycemia both during and after meals [20, 21].

The introduction of basal insulin analogs into therapy has resulted in a series of clinical studies that provide us with data on the most effective way to use these insulins in the treatment of T1DM and type 2 DM (T2DM) [22].

The effect of insulin analogs on the level of HbA1c, both fast-acting and long-acting, was reviewed through two significant analyses (Cochrane Reviews) [23, 24]. In an analysis that included 49 randomized clinical trials with rapid-acting insulin analogs compared to human insulins, a mean difference in HbA1c level of -0.1% was calculated in favor of analogs in T1DM. However, it is important to emphasize that the studies with basal insulins are designed in principle so that the dose is titrated according to the algorithm, with the aim of reaching the target level of HbA1c in all patients, hence a similar level of HbA1c achieved is not entirely unexpected [25].

Three clinical studies have compared an insulin regimen with insulin analogs (both rapid-acting and basal) with a regimen with human insulin alone in patients with T1DM [26–28]. In the largest of these three studies, a basal-bolus regimen with insulin aspart and insulin detemir was compared with a regimen with regular and NPH human insulin in 595 patients with T1DM for 18 weeks [26]. At the end of the study, the mean HbA1c level was lower in the aspart/detemir group than in the regular/NPH insulin group (7.88% vs. 8.11%; $p < 0.001$).

In a smaller but longer study with 56 patients with T1DM, a treatment regimen with insulin lispro and insulin glargine achieved a mean HbA1c level of 7.5% after 32 weeks compared to a mean HbA1c level of 8% achieved in patients treated human regular and NPH insulin [27]. A third study with a cross-over design, conducted in 28 adolescents with T1DM, showed no statistically significant differences in the achieved level of HbA1c among subjects treated with the combination of lispro/glargine compared with regular/NPH human insulin for 16 weeks (8.7% vs. 9.1%; $p = 0.13$) [28].

Our results showed a decrease in HbA1c levels after the introduction of insulin analog therapy. After three months of insulin aspart therapy, there was a non-significant decrease in the level of HbA1c. After the introduction of insulin glargine and three-month therapy with a combination of insulin analogs (aspart/glargine), there was a further significant decrease in the level of HbA1c.

After the first three months of therapy, a significant reduction in PPG was noted after all three main meals. There were no significant differences in FBG before meals, before bed, and at night, as well as in MBG values in the profile. The variability of daily BG was significantly lower. The mean PI in BG after a meal (the mean value of the difference between postprandial and preprandial BG) significantly decreased after the introduction of insulin aspart as prandial insulin. There are significant differences after all three meals individually and in the total PI during the day. In the second three-month period with aspart/glargine therapy, there are no further statistically significant differences in the level of BG increase after a meal.

After the introduction of both insulin glargine and three-month therapy with a combination of insulin analogs (aspart and glargine), there was a further significant reduction of most glycemic values in the daily profiles, especially FBG, MBG in the profiles, as well as the variability of daily glycemic values.

While improvements in HbA1c levels in the studies have been clearly linked to a lower incidence of the classic microvascular complications of diabetes [1], there is increasing evidence that a reduction in the incidence of macrovascular complications (ischemic heart disease, cerebrovascular disease, and peripheral vascular disease) may be more strongly related to the level of PPG, especially in T2DM. Isolated postprandial hyperglycemia (PPG > 7.8 mmol/L) in patients with normal FBG and optimal HbA1c (< 6.1%) doubles the risk of mortality from cardiovascular diseases [29]. Moreover, in large studies, in populations consisting of both DM and non-diabetics, the level of PPG was associated with total and cardiovascular mortality [30, 31].

In a review of published studies comparing rapid-acting insulin analogs with human insulin, in basal-bolus therapy, rapid-acting insulin analogs had a greater effect on PPG in each of the studies, with a lower PPG level compared to human insulin between 0.6 and 2.0 mmol/L [25]. In one of the longest studies (32 weeks) comparing a regimen with insulin analogs (lispro/glargine) to human insulins (regular/NPH human insulin), a significantly lower PPG area under the curve (AUC) was noted with the analog regimen (75 vs. 88 mmol/L/h; $p = 0.002$) [27].

Our results are in accordance with most of the results from the literature, i.e., the introduction of fast-acting insulin analogs into therapy significantly improves prandial glycemic regulation. In our results, this is reflected in a significant reduction in the level of PPG after all three main daily meals in the daily glycemic profiles, as well as in the decrease in the PI in BG after all three meals individually and in the total average PI in BG during the day.

A review analysis of studies (Cochrane Review) found a lower median incidence of severe hypoglycemic episodes with rapid-acting insulin analogs *per* 100 patients *per* year (21.8; range 0–247.4) compared with human insulin (46.1; range 0–544) [24]. Likewise, analysis of studies with long-acting insulin analogs found a significantly lower risk of nocturnal hypoglycemia in patients treated with insulin glargine ($p = 0.00003$) and insulin detemir ($p < 0.00001$) compared to NPH insulin. The risk of symptomatic hypoglycemia was also lower for insulin glargine compared to NPH insulin ($p = 0.005$) and for insulin detemir ($p = 0.00003$) [23]. The rate of severe hypoglycemia was lower with both basal insulin analogs compared with NPH insulin, although the threshold for statistical significance was not reached ($p = 0.2$) [32].

Our results showed a significant reduction in the number of hypoglycemias after the introduction of insulin analogs into therapy. The total number of hypoglycemias is lower after three months and the introduction of insulin

aspart into therapy (a finding slightly above the significance limit, $p = 0.06$), and it decreases especially after the introduction of insulin glargine into therapy, i.e., the total number of hypoglycemias expressed as the number of hypoglycemias *per* patient *per* month is lower at the end of the study and compared to the first three months of therapy, and especially compared to the period before the introduction of analogs in therapy ($p < 0.001$). There are significant differences, first of all, in the number of symptomatic hypoglycemia, which decreases after three months of therapy and at the end of the sixth month. The number of asymptomatic hypoglycemias was lower at the end of the study compared to the first three months of therapy and compared to the beginning of the study, while there was no difference in the number of asymptomatic hypoglycemias after three months compared to the beginning. This led to an increase in satisfaction with therapy and a reduction of the perception of both hyperglycemia and hypoglycemia, as we previously reported [33].

These data can be seen as part of the overall reduction in the number of hypoglycemias, both symptomatic and asymptomatic. They can be interpreted by better recognition of hypoglycemia described in patients in whom good control and avoidance of hypoglycemia improves the autonomic response to hypoglycemia and its recognition [34–37]. This effect takes some time to manifest itself; therefore, it was possibly more significant in the second half of our study. The number of nocturnal hypoglycemias also showed no changes after the first three months of therapy. Still, after the introduction of insulin glargine therapy, the number of nocturnal hypoglycemias was significantly lower compared to the moment before its inclusion and to the beginning of the study, i.e., to the period of therapy with human insulin alone ($p < 0.001$). This prominent and very significant advantage of insulin glargine compared to human basal insulins agrees with earlier reports, both worldwide and in our setting [21, 38]. In this context, the fact that at the end of the study, the level of almost all glycemia in the daily profiles was lower compared to the period after three months, except for night glycemia, should be seen as an advantage of insulin glargine in terms of its better safety, because the night period in the context of the phenomenon hypoglycemia is certainly the most sensitive and dangerous for patients. Reduction of the number of hypoglycemias is also connected with the variability of daily glycemia, which was significantly lower after the insulin analogs therapy, especially after the period of the introduction of glargine in therapy [39].

Our results showed some positive changes in the BW of our patients, which was lowest after the sixth month, and a difference at the end compared to the BW before the introduction of insulin glargine is statistically significant ($p < 0.01$), and also compared to the initial BW ($p < 0.05$). The same applies to the difference in BMI levels. The fact that the improvement of glycoregulation in the first three months was not accompanied by a significant change, i.e., a significant increase in BW, is positive for insulin aspart. An additional and even more significant improvement in glycoregulation after the introduction of insulin glargine, which was accompanied by a significant drop in BW, justifies the claims that basal insulin analogs, compared to NPH insulin, have a significantly more favorable effect on BW patients. The neutrality with regard to BW of new insulin preparations, which is also noted in our patients, is one of the significant advantages of insulin analogs compared to human insulins [40].

The fact that we recorded a discrete but significant drop in BW in our patients with a clear and very significant improvement in glycoregulation can also be interpreted through the analysis of the total daily dose of insulin. Namely, our results show a decrease in the total daily dose of insulin after three months of therapy (p = ns) and at the end of the study ($p < 0.01$ compared to three months and $p < 0.001$ compared to the beginning of the study). Achieving the same or even better degree of glycoregulation (as in our study) with lower doses of insulin is another advantage of insulin analogs. The dose reduction in our study is primarily due to the reduction of bolus and rapid insulin. The bolus dose at the beginning of the study fell after three months and even more at the end of the study (all these differences are highly statistically significant, $p < 0.001$). In contrast, the dose of basal insulin increased from the initial after three months ($p < 0.001$) and then further (p = ns compared to the value after three months). It can be concluded that the effect of fast, bolus insulin is potentially that which we associate with the increase in appetite, the increase in food intake, and the consequent increase in BW. The fact that this effect is manifested above all after the change of basal insulin and the introduction of insulin glargine in therapy confirms that good basal insulinization is necessary, which will enable good initial FBG and even insulinization between meals. In this way, bolus doses can be adjusted to the planned caloric intake, i.e., the size of the meal. That way there is no delay in the effect of bolus insulin after a meal and the need for additional food intake, which can potentially lead to an increase in BW. This is supported by a significant reduction in the variability of daily glycemia, which was recorded after three months of therapy and at the end of the study. Improvement of BG control with IIT with insulin analogs was accomplished without weight gain, like in some previous reports [41].

It has been pointed out that the state of low-grade chronic inflammation, followed by an increase in the circulatory level of inflammatory markers, primarily CRP, represents a risk for the development of various chronic complications. The US Centers for Disease Control and Prevention and the American Heart Association indicate that people with CRP values in the upper tertile for the adult population (> 3.0 mg/L) have double the cardiovascular risk compared to people whose CRP value is less than 1.0 mg/L [42].

Our results show a statistically significant decrease in CRP levels in the first three months, which is maintained until the end of the study and in the following three months. This decrease in CRP is primarily associated with the reduction of prandial stress, i.e., the value of PPG and the PI of BG. Studies support evidence that acute

hyperglycemia during a hyperglycemic clamp [43] or in the postprandial state [44] can increase the production of inflammatory cytokines, such as interleukin (IL)-6, tumor necrosis factor (TNF)-α and IL-18, and the concept that atherosclerosis is an inflammatory disease in diabetes has been confirmed [45].

The noted decrease in CRP levels can also be related to the finding of a discrete reduction in BW and a decrease in the total daily dose of insulin, which corresponds to previous report [46] in which intensive insulin therapy is also correlated with complex changes in inflammatory markers, which are potentially dependent on the degree of BW gain, and may represent a risk for the development of atherosclerosis. In this subgroup analysis from the DCCT study, among those on IIT, high sensitivity CRP (hsCRP) levels increased in those with the highest BW gain, while it decreased among those in the lowest third of BW gain. It is stated that IIT in patients with T1DM decreased the level of soluble intercellular adhesion molecule-1 and increased the levels of soluble TNF receptor 1 and hsCRP among those who increased BW. These data show that the effect of IIT on inflammation is complex and, since hsCRP is an inflammatory risk factor, it is suggested that the risk of atherosclerosis among diabetic patients may be influenced by the degree of gain in BW when on IIT [46].

Conclusion

Treating patients with T1DM with insulin analogs (insulin aspart and insulin glargine) in intensified insulin therapy leads to improvement of blood glucose control with a decrease in hypoglycemia, body weight, a dose of insulin, and C-reactive protein level.

Conflict of interest

The authors declare no conflict of interest.

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