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Original Research

The Effect of Type and Daily Doses of Insulin to Treatment Success in Type 2 Diabetes Patients who are Receiving Basal-bolus Insulin Therapy

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Abstract

Objectives: The present study aims to compare different types of insulin concerning treatment success and insulin dose requirement in type 2 diabetes patients who were receiving basal-bolus insulin therapy and to evaluate the causes of treatment failure despite high doses of insulin.

Methods: In our retrospective study, 198 type 2 diabetes patients who were receiving basal-bolus insulin therapy included. Patients were divided into three groups according to the insulin types (Group 1: short and long-acting analogue insulin users (n=83), Group 2: short and long-acting human regular insulin users (n=58), Group 3: human regular insulin + long-acting analogue insulin users (57)). Demographic data and daily insulin doses were recorded from the patient follow-up files. These data and the rates of achievement of the target HbA1c levels were also compared between groups. In addition, insulin doses of the patients whose glycemic targets could and could not be achieved were compared.

Results: In this study, 123 (62.1%) of the 198 patients were female and 65 (47.9 %) were male. The mean age of the three groups was 55.81±8.1, 58.3±8.9, 58.3±8.8, respectively. HbA1C values were 8.72±1.65% in group 1, 9.0±1.98% in group 2 and 9.05±2.24% in group 3. The rates of achievement HbA1c value below 7% were 27.7% in analogue insulin group, 25.9% human regular insulin group and 31.6% in regular + analogue insulin group ($p > 0.05$). There were no significant differences in daily basal and bolus insulin doses, total daily and per kg insulin doses and basal-bolus rates between groups. Higher total daily insulin doses were determined in patients who could not achieve target glycemic values than achieved it in group 1 and 2. Higher basal insulin doses were determined in patients who could not achieve target glycemic values than could achieved it in group 3.

Conclusion: In our study, in which we did not find any significant difference in the dose analysis between analogue and regular insulin, the findings showed that high insulin doses might not be sufficient for glycemic control. The underlying causes should be investigated and correctible reasons should be eliminated in these patients.

Keywords: High insulin dose; insulin; type 2 diabetes.

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Diabetes is a complex disease requiring multifactorial risk-reducing strategies and continuous medical care beyond -glycemic control.[1] There were 451 million diabetic individuals in 2017, while 5 million people died of diabetes, and healthcare expenditures for diabetes patients were approximately $850 million.[2] The prevalence of diabetes in our country was evaluated with the Turkish Epidemiology Survey of Diabetes, Hypertension, Obesity, and Endocrine Diseases (TURDEP I and II). It was seen that the prevalence of diabetes in our country was 7.7% in TURDEP I survey conducted in 1998-1999 and reached 13.7% in the TURDEP II survey conducted in 2010.[3, 4]

Current guidelines recommend that diabetes patients are kept as close as possible to normoglycemia. Although several therapy options were developed to achieve this goal, insulin continues to be the strongest antihyperglycemic agent in type 2 diabetes. In the surveys conducted, it has been recommended to add basal insulin to oral agents for patients that cannot be controlled sufficiently with antidiabetic agents. If it is not possible to establish or maintain glycemic control under this therapy, short-acting insulin should be added for switching to basal-bolus insulin therapy.[1]

Theoretically, basal-bolus insulin therapy is the ideal therapy for individualization of insulin therapy because dosage timing is more physiological and the appropriate dose can be adjusted more easily. However, we see treatment failure although we use higher insulin doses in most of the patients in our everyday practices. The reasons generally include the patients' failure to comply with their diets, therapies and follow-ups; intercurrent infections; other medications taken; additional endocrine diseases or insulin resistance syndromes. In addition to all these factors, the aims of our study were to find out the effects of insulin types chosen and insulin doses applied on treatment success in patients for whom glycemic control cannot be achieved despite high doses of insulin, to compare analogue and regular insulin concerning treatment success and daily insulin dose requirement, and put forward the relation of total daily insulin doses with factors, such as the patient's age, duration of diabetes, education level and HbA1c levels. Thus, we conducted a retrospective analysis of patients that received basal-bolus insulin therapy in our center.

Methods

In our study, we retrospectively assessed 198 patients who were admitted to the endocrinology polyclinic as outpatients between 2007-2012 and then visited for follow-up at least twice, and who meet the following inclusion criteria:

being diagnosed with Type 2 diabetes, being between 30-70 years of age, and receiving basal-bolus insulin therapy alone or with Metformin for at least six months. Patients who have diabetes types other than Type 2, are pregnant, have additional endocrine diseases that impair diabetes regulation (e.g., hypothyroidism, hyperthyroidism, pheochromocytoma, Cushing, acromegaly), use pancreatotoxic medication or corticosteroid medication that may impair glucose tolerance, have end-stage renal failure, malignancy and liver failure were not included in the study.

Patients were divided into three groups according to the different insulin types they received (Group 1: short- and long-acting analogue insulin users (n=83), Group 2: short- and long-acting human regular insulin users (n=58), Group 3: regular insulin + long-acting analogue insulin users (57)).

Information about the patients included in this study, such as gender, age, education level, duration of diabetes, duration of intensive therapy, body weight, body mass index, average of last 3 HbA1c values, latest type of insulin received, and total, basal and bolus insulin dose per day and per kilogram- was taken from their files for their latest applications and recorded. This information was compared among groups with statistical methods.

ADA 2018 criteria were considered for a diabetes diagnosis. Body mass index was calculated using the formula body weight (kg)/height $(m)^2$. The patients' average of HbA1c values in the last three applications were calculated and recorded. HbA1c levels of all patients were found in our hospital's laboratory with HPLC (High-performance liquid chromatography) method. Using the information on the latest insulin doses received by the patients and their body weight; daily basal insulin dose, daily bolus insulin dose, total daily insulin dose, total insulin dose per kilogram, basal insulin dose per kilogram, bolus insulin dose per kilogram, daily basal insulin/total insulin ratio and daily bolus/total insulin ratio were calculated and recorded.

Statistical Analysis

During the evaluation of the findings obtained from this study, SPSS 21.0 statistical package program was used for the statistical analyses. Descriptive statistical methods (Frequency, Percentage, Standard Deviation) were used in the evaluation of the study data. In the analysis of quantitative data, ANOVA (Tukey test)/Kruska-Wallis, Mann-Whitney U test and unpaired t-test were used. In the analysis of qualitative data, a chi-squared test (and Fisher test when conditions for the chi-squared test could not be met) was used. In the comparison of two quantitative data, Pearson Correlation Analysis was used for cases of the normal distribution, and Spearman Correlation Analysis was used for non-normal distribution cases. Wilcoxon signed-rank test was used in the inter-group comparison of parameters.

The results were evaluated to be in the confidence interval of 95% and had a significance at the level of p<0.05.

Findings

In this study, 123 (62.1%) of the 198 patients were female and 65 (47.9%) were male. According to the type of insulin they use, there were 83 patients receiving short- and long-acting analogue insulin (Group 1), 57 patients were receiving short- and long-acting human regular insulin (Group 2) and 58 patients were receiving short-acting regular and long-acting analogue insulin (Group 3). The mean age of the groups was 55.81±8.1, 58.3±8.9, 58.3±8.8, respectively. Concerning education level, the rate of primary school graduates was significantly high in all groups. There were no significant statistical differences among groups concerning Metformin usage (group 1: 38.6%, group 2: 34.5%, group 3: 34.6%, p: 0.220). Age, gender, weight, BMI, duration of diabetes, duration of intensive therapy and creatinine distribution did not show a significant difference among all three groups (p>0.05) (Table 1).

HbA1c levels were 8.72%±1.65 analogue insulin group, 9.02%±1.98 in regular insulin group, and 9.05%±2.24 in regular insulin + analogue insulin group. There was no significant difference among all three groups concerning Hba1c levels (p>0.05). The rates of achieving HbA1c values below 7% were 27.7% in the analogue insulin group, 25.9% human regular insulin group and 31.6% in the regular + analogue insulin group (p>0.05) (Table 1).

When insulin doses were analyzed, daily bolus insulin dose, daily basal insulin dose, total daily insulin dose, total insulin, daily basal/total insulin ratio and daily bolus/total insulin ratio did not show a significant difference among all three groups (p>0.05) (Table 2).

There was a negative significant correlation between total daily insulin dose and age (p<0.05). There was a positive significant correlation between total daily insulin dose and duration of diabetes, duration of intensive therapy, HbA1c, BMI value and weight (p<0.05) (Table 3).

There was a positive significant correlation between total insulin dose per kg and duration of diabetes, intensive therapy duration, weight and HbA1c (p<0.05). There was no significant correlation between total insulin and age, creatinine and BMI values (p>0.05) (Table 3).

Insulin doses for patients that could achieve the target of HbA1c 7% were analyzed for each group. Accordingly, daily bolus insulin dose, daily basal insulin dose, total daily insulin dose, total insulin dose per kilogram, basal insulin dose (IU/

Table 1. Demographic and characteristic data

	Patients Receiving Basal-bolus Analogue Therapy Avg.±s.s./n-%			Patients Receiving Basal-bolus Regular Therapy Avg.±s.s./n-%			Basal-bolus Mix (Analogue+Regular) Insulin Avg.±s.s./n-%			p
Age	55.81	±	8.1	56.3	±	8.9	58.3	±	8.8	0.235
Gender										
Female	46		55.4%	41		70.7%	36		63.2%	0.181
Male	37		44.6%	17		29.3%	21		36.8%	
BMI (kg/m^2)	32.83	±	5.36	34.44	±	8.57	33.01	±	4.94	0.063
Weight (Kg)	80.1	±	15.2	86.2	±	21.1	86.3	±	14.8	0.051
Education										
Illiterate	13		15.7%	16		27.6%	11		19.3%	>0.05
Primary School	52		62.7%	34		58.6%	36		63.2%	
Secondary School	6		7.2%	2		3.4%	5		8.8%	
High School	6		7.2%	6		10.3%	5		8.8%	
University	6		7.2%	0		0.0%	0		0.0%	
Duration of Diabetes (Year)	11.20	±	6.66	11.71	±	7.81	13.75	±	7.41	0.112
Duration of Intensive Therapy (Year)	3.48	±	2.00	3.69	±	2.24	3.75	±	1.60	0.057
Hba1c	8.72	±	1.65	9.02	±	1.98	9.05	±	2.24	0.532
HbA1c										
≤7	23		27.7%	15		25.9%	18		31.6%	0.784
>7	60		72.3%	43		74.1%	39		68.4%	
Creatinine	0.80	±	0.18	0.83	±	0.22	0.80	±	0.19	0.565

ANOVA (Tukey test) Kruskal-Wallis (Mann-Whitney U test)/Chi-squared test; BMI: Body Mass Index Kg: kilogram.

Table 2. Analysis of insulin doses in all groups

	Long+Short-Acting Analogue Insulin Avg.±s.s.	Long+Short-Acting Regular Insulin Avg.±s.s.	Basal-bolus Mix (Analogue+Regular) Insulin Avg.±s.s.	p
Daily Bolus Insulin Dose (IU/day)	42.42±17.70	48.40±20.90	45.28±19.4	0.192
Daily Basal Insulin Dose (IU/day)	26.55±9.72	27.28±12.72	27.28±12.2	0.098
Total Daily Insulin Dose (IU/day)	68.98±25.43	75.67±28.67	72.56±28.9	0.357
Total ınsulin (kg/IU/kg)	0.87±0.30	0.89±0.32	0.85±0.33	0.735
Daily Basal/Total Insulin Ratio	0.39±0.06	0.36±0.09	0.38±0.07	0.087
Daily Bolus/Total Insulin Ratio	0.61±0.06	0.64±0.09	0.62±0.07	0.087
Bolus ınsulin IU/kg	0.54±0.22	0.57±0.21	0.53±0.22	0.576
Basal ınsulin IU/kg	0.33±0.10	0.33±0.17	0.32±0.14	0.842

ANOVA, Kg: kilogram IU: International Unit.

Table 3. Relation of total daily insulin doses according to body weight with age, duration of diabetes, duration of intensive therapy, Hba1c, creatinine, BMI and weight

	Age	Duration of Diabetes (Year)	Duration of Intensive Therapy (Year)	Hba1c	Creatinine	BMI	Weight (Kg)
Total Daily Insulin Dose (IU/day)							
r	-0.144	0.178	0.323	0.291	0.009	0.359	0.348
p	0.042	0.012	0.000	0.000	0.899	0.000	0.000
Total Insulin (kg/IU/kg)							
r	-0.092	0.162	0.299	0.270	-0.028	-0.051	-0.145
p	0.200	0.023	0.000	0.000	0.696	0.473	0.041
Pearson correlation							

IU: International Unit Kg: kilogram BMI: Body mass index.

kg) and bolus insulin dose (IU/kg) in patients that could not achieve the target in Group 1 and Group 2 were significantly higher (p<0.05). Daily basal/total insulin ratio and daily bolus/total insulin ratio did not show a significant difference in patients with HbA1c ≤7% and >7% (p>0.05) (Tables 4, 5).

Daily bolus insulin dose, daily basal insulin dose, total daily insulin dose, total insulin value, daily basal/total insulin ratio and daily bolus/total insulin ratio and bolus insulin value in patients that could and could not achieve the target in Group 3 did not show a significant difference

Table 4. Comparison of the insulin doses of patients with HbA1c ≤7% and >7% in short- and long-acting analogue insulin group

Patients Receiving Long+Short-Acting Analogue Insulin	HbA1c ≤7% (n=21) Avg.±s.s.	HbA1c >7% (n=62) Avg.±s.s.	p
Daily Bolus Insulin Dose (IU/day)	31.14±8.82	46.24±18.35	0.001
Daily Basal Insulin Dose (IU/day)	20.33±5.88	28.66±9.89	0.000
Total Daily Insulin Dose (IU/day)	51.48±13.08	74.90±25.93	0.000
Total Insulin (kg/IU/kg)	0.68±0.14	0.93±0.31	0.000
Daily Basal/Total Insulin Ratio	0.40±0.06	0.39±0.06	0.590
Daily Bolus/Total Insulin Ratio	0.60±0.06	0.61±0.06	0.590
Bolus Insulin (IU/kg)	0.41±0.10	0.58±0.24	0.002
Basal Insulin (IU/kg)	0.27±0.07	0.36±0.10	0.001

Unpaired t-test IU: International Unit Kg: kilogram.

Table 5. Comparison of insulin doses of patients with HbA1c ≤ 7% and > 7% regular insulin + NPH group

Patients Receiving Long+Short-Acting Regular Insulin (n=58)	HbA1c ≤7% (n=12) Avg.±s.s.	HbA1c >7% (n=46) Avg.±s.s.	p
Daily Bolus Insulin Dose (IU/day)	37.67±17.37	51.20±21.00	0.045
Daily Basal Insulin Dose (IU/day)	19.58±9.89	29.28±12.70	0.017
Total Daily Insulin Dose (IU/day)	57.25±24.27	80.48±27.98	0.011
Total Insulin (kg/IU/kg)	0.69±0.27	0.95±0.31	0.000
Daily Basal/Total Insulin Ratio	0.35±0.08	0.37±0.10	0.525
Daily Bolus/Total Insulin Ratio	0.65±0.08	0.63±0.10	0.525
Bolus Insulin (IU/kg)	0.46±0.21	0.60±0.21	0.045
Basal Insulin (IU/kg)	0.23±0.09	0.35±0.18	0.027

Unpaired t-test IU: International Unit Kg: kilogram NPH: Neutral Protamine Hagedorn.

among all three groups (p>0.05). The basal insulin value of patients that could not achieve the target was significantly higher than patients that could achieve the target (p<0.05) (Table 6).

Discussion

Type 2 diabetes is a disease with a progressive increase in beta-cell injury and beta-cell beta-cell loss over the years. With the decrease of total insulin secretion capacity over the years, secondary chronical and ever-worsening hyperglycemia is developed, which may also increase the impairment in insulin secretion.[5] Most of the patients need insulin therapy to achieve glycemic control in the advanced stages of the disease. However, achieving and maintaining long-term glycemic control in Type 2 diabetes patients is very difficult because it is affected by several factors. Both patients and doctors who plan the therapy contribute to poor glycemic control.

In this study, we tried to evaluate factors affecting glycemic control, particularly based on the analysis of insulin doses, in three groups of patients receiving intense insulin therapy with different insulin types.

In our study, average Hba1c rates of the patients were 8.72%±1.65, 9.02%±1.98 and 9.05%±2.24 for analogue insulin, regular insulin and regular + analogue insulin therapy groups, respectively, and it was seen that glycemic control was not sufficient.

When the education levels of all three groups were evaluated, the rate of primary school graduates was significantly high (62.7%, 58.6% and 63.2%, respectively) (p>0.05). One of the studies on this issue shows that compliance is more difficult and blood glycemic level monitorization is less frequent in groups with low education levels and language problems.[6] Low education level might have a role in the failure to achieve targeted Hba1c values.

The average duration of diabetes was 12.2±7.29 years in all three groups without a significant difference between the duration of diabetes therapy; however, the average duration of intensive therapy was 3.54±1.93. A study conducted by Khattab et al. on factors affecting poor glycemic control found out that duration of diabetes more than seven years was related to poor glycemic control.[7] On the other hand, starting insulin therapy in the early period is important for protecting beta-cell reserve. It was observed in several

Table 6. Comparison of insulin doses of patients with HbA1c ≤ 7% and > 7% in regular insulin + long-acting analogue group

Patients Receiving Regular Insulin+Long-Acting Analogue Insulin (n=57)	HbA1c ≤7% (n=13) Avg.±s.s.	HbA1c >7% (n=44) Avg.±s.s.	p
Daily Bolus Insulin Dose (IU/day)	44.85±25.47	45.41±17.71	0.928
Daily Basal Insulin Dose (IU/day)	22.46±8.30	28.70±12.92	0.107
Total Daily Insulin Dose (IU/day)	67.31±32.86	74.11±27.97	0.462
Total Insulin (kg/IU/kg)	0.75±0.30	0.87±0.33	0.235
Daily Basal/Total Insulin Ratio	0.36±0.08	0.39±0.07	0.143
Daily Bolus/Total Insulin Ratio	0.64±0.08	0.61±0.07	0.143
Bolus Insulin (IU/kg)	0.50±0.25	0.54±0.21	0.595
Basal Insulin (IU/kg)	0.25±0.07	0.34±0.15	0.047

Unpaired t-test IU: International Unit Kg: kilogram.

studies that endogenous insulin secretion and insulin sensitivity could be improved with intensive insulin therapy in the early period.[8, 9] In line with this information, it can be considered that long duration of diabetes and late start of insulin therapy contributed to poor glycemic control in our study group.

Current guidelines indicate the targeted HBA1c value ≤7% in type 2 diabetes patients; however, less stringent target values are recommended for people with severe hypoglycemia history, limited life expectancy, advanced level of micro- and macro-vascular complications, comorbidities and long duration of diabetes, who cannot achieve the target despite diabetes training, appropriate blood glucose follow-up and effective doses of multiple hypoglycemic agents, including insulin. In our study, the rate of patients achieving Hba1c level ≤7% was 28% among all patients. When the three groups included in this study were evaluated separately, the rate of achieving target values was 27.7% for analogue insulin, 25.9% with human insulin, and 31.6% for the combined therapy group. There were no statistically significant differences among the three groups in this respect.

The review by Giugliano et al. evaluated rates of achieving various HBA1c targets of 53 randomized controlled studies, including patient groups receiving different therapy regimes with insulin analogues (basal, prandial, biphasic, basal-bolus). In the analysis of eight studies, where patients receiving intensive basal-bolus insulin therapy were evaluated, rates of achieving Hba1c <6.5% were 27.8%, <7% as 52.3%, <7.5% as 75%, and <8% as 87%.[10] Fonseca et al.[11] compared regular insulin + NPH and regular insulin + glargine in their study, and the rates of achieving Hba1c level ≤ 7% were 34.2% with regular insulin + glargine and 24.4% with regular insulin + NPH, similarly to our study.

Factors of low achievement rates in diabetes patients receiving intensive therapy include the patients' ignoring administration of non-pharmacological therapies while they are under pharmacological therapies, difficulty in following the therapies and errors in the planning of therapy. Especially in the planning of basal-bolus insulin therapy, the patient should be provided with sufficient training on subcutaneous insulin administration techniques, dosage times, meal times and hypoglycemia risks by diabetes training nurses and dieticians. Patients under insulin therapy who visit or are inpatients in our polyclinic are provided with diabetes training. However, the patients' receipt of diabetes training, compliance with diet/exercise and hypoglycemia frequency could not be evaluated as our study was conducted retrospectively and patient files did not contain sufficient information. An important element of correct planning of insulin therapy is that total insulin doses recommended to patients per day and per kg are calculated correctly, basal/bolus ratio is planned similarly with physiological secretion and titrated correctly over time.

When the insulin doses of the three groups were evaluated, we found that insulin types did not show any difference in terms of daily insulin doses (Table 2). In the study by Fonseca et al., 100 patients receiving regular insulin + NPH and regular insulin + insulin glargine were evaluated, and the rates of achieving HbA1c <7% and insulin doses were similar in both groups (basal dose 36.4±26.5 IU/day, bolus 37.1±28.4 IU/day, total dose 73.5 IU/day in glargine group; basal 30.2±22.8 IU/day bolus: 34.0±24 IU/day, total: 64.1 IU/day in NPH group).[11] In the study conducted by Meyer et al., where glulisine+glargine insulin users and human regular + glargine insulin users among 180 inpatients were compared, A1c values of groups were 7.7±1.8 and 7.7±1.7, respectively, and total daily and bolus insulin doses were similar (total daily insulin 69±33 vs. 71±45 IU/day, bolus insulin 36±18 vs. 38±24 IU/day).[12] In the study by Yokahama et al., one group received glargine and the other received NPH as basal insulin in addition to short-acting analogue insulin, and the insulin doses were compared. Daily insulin dose in the glargine group was 42±18 IU with an average basal insulin ratio of 48%, and the total dose in the NPH group was 38±16 with an average basal insulin ratio of 28%.[13] In the study by Cai et al., the basal/total insulin ratio was 23% in the patient group that could achieve the targeted fasting blood glucose values. Total insulin doses used were lower compared to Western studies (38 IU/day, 0.58 IU/kg).[14] Total doses vary between 0.31 IU/kg-0.62 IU/kg in other Far-Eastern studies.[15, 16] In our study, insulin doses used in patients who could achieve HbA1c values below 7% were 0.68±0.14 IU in the analogue insulin group, which was 0.69±0.27 IU in regular insulin group and 0.75±0.3 IU in regular + long-acting analogue insulin group. These doses are more compliant with Western studies. Many studies have shown that racial and ethnic factors are effective in the pathogenesis of diabetes. Insulin resistance is more frequent in Latins, while beta-cell dysfunction is more common in the Far East.[17]

Many studies argue that the basal/bolus ratio in insulin regime with frequent intervals should be 50/50%, which is the closest ratio to physiological secretion.[18, 19] Basal/bolus ratio was ~49/51% in the study by Bergenstal et al., 48/52% in the study by Rosenstock et al., and 50/50% in the study conducted by Fonseca et al.[11, 20, 21] In our study, the basal/bolus ratio was approximately 40/60% in patients with Hba1c values below 7%.

Another finding revealed in our study was that the total in-

sulin dose in patients that could not achieve the targeted Hba1c value was significantly higher than patients that could achieve the target. Moreover, the findings showed high daily insulin doses were related to young age, long duration of intensive therapy, high HbA1c, high BMI value and high body weight. Duration of diabetes, BMI, fasting and preprandial blood glucose levels and HbA1c levels were also higher in the group receiving a high dose of total daily insulin in the study by Cai et al.[14] They interpreted this as the need for higher insulin in patients with poor glycemic control due to insulin resistance and beta-cell dysfunction. However, they did not discuss why glycemic control could not be achieved although high doses were used.

In many major studies, such as UKPDS (United Kingdom Prospective Diabetes Study), beta-cell dysfunction and insulin resistance in patients under Type 2 diabetes therapy were related to higher exogenous insulin need.[22] Although the term "insulin resistance" has been used since the discovery of insulin in 1922, it was put forward more clearly in studies with patients observed to be in need of very high doses of insulin in the 1930s.[23]

There are several methods used to measure insulin resistance; however, total daily insulin dose can give an idea in a simpler way. As a practical approach, an insulin need <1 IU/kg/day shows that insulin sensitivity is normal. An insulin need above 2 IU/kg per day shows the presence of severe insulin resistance. Response to insulin therapy is very low in doses above 200 IU/day.[24] The need for doses above 3 IU/kg per day are called extreme insulin resistance, which is a syndromic table, while most of the patients are non-obese and generally have BMI <25 kg/m^2.[25]

The reasons for the need for higher doses of insulin include severe insulin resistance syndromes (Type A, B, C), medications, other endocrine diabetes reasons, non-compliance with insulin therapy and non-pharmacological therapies, factitious reasons, such as secondary gain, pregnancy, accompanying severe diseases, genetics (e.g., familial lipodystrophy syndromes), hypersensitivity, HIV (HIV-related lipodystrophy), gustatory conditions (eating disorders characterized with overeating), rarely increased insulin clearance, impaired insulin absorption or idiopathic reasons.[26] Obesity, which has become an epidemic disease, is the most common reason of increasing insulin need today. It is thought that the injection of a very high quantity of insulin into the subcutaneous tissue at one delays or impairs insulin absorption, which increases the insulin need and leads to a vicious circle. This hypothesis was proved in the study that Binder et al.[27] conducted on rats and put forward indirectly in human experiments. Dandona et al. administered low doses of insulin infusion (50-60 IU/day) on six patients in need of high doses of insulin (120-300 IU/day) and show that glucose homeostasis occurred. Based on these results, they argued that the need for high doses of insulin might arise from possible impairments in insulin absorption from the subcutaneous tissue at the injection point as well as from insulin resistance.[28] It was also observed in a study that patients' need for daily high doses of insulin decreased when their insulin preparations were changed with more concentrated insulin preparations (U-500 insulin).[24]

Patients who have additional endocrine diseases or use medication that may impair glycemic control were not included in our study. Therefore, when our patient group is evaluated, non-compliance with insulin therapy and non-pharmacological therapies, factitious reasons, such as secondary gain, insulin resistance syndromes and hypotheses related to absorption impairments come to the forefront as the reasons why glycemic control could not be achieved although high doses were used. At this point, the most important issue to be emphasized is that patients should be provided with sufficient training and their awareness should be raised for compliance with insulin therapy. Regimes with fewer injections should be recommended for patients that have difficulties in compliance despite these. Considering hypotheses related to absorption impairments, it may be useful to administer high volumes of injections by dividing them into two different parts of the body or to divide the total basal dose into morning and evening injections.

In consequence, insulin therapy, which has been repeatedly proven to be the most effective method of ensuring glycemic control in many studies, maybe unsuccessful when not used for the right patient in the right way. This study tries to emphasize the importance of correct adjustment of total daily dose quantity and dose distribution in the planning of insulin therapy and starting insulin therapy as early as possible. In our study, which we did not find any significant difference in the dose analysis between selected types of insulin, the findings showed that high insulin doses might not be sufficient for correct glycemic control. Therefore, the underlying reasons should be sought in patients for whom glycemic control cannot be achieved although high doses are used, correctible reasons should be eliminated, and different strategies should be tested in the number and timing of injections without increasing doses, by taking absorption impairments into consideration.

Disclosures

Ethics Committee Approval: Approval was obtained from Şişli Etfal Training and Research Hospital Ethics Committee for our study (DATE: 23/10/2018 and NO: 2149).

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