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The effects of short-acting analogue insulins on body weight in patients with type 2 diabetes mellitus

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Aim: To investigate the effects of short-acting analogue insulins on weight, and to demonstrate the difference between analogues.

Materials and methods: Our study included patients who have used only intensive insulin therapy with metformin. Those who took other oral antidiabetics, other insulin derivatives, or different insulin combinations were excluded from the study because of the adverse effects on patients' weights.

Results: Our study included 118 patients who used insulin glargine with short-acting analogue insulins, i.e. insulin aspart (38 patients), insulin lispro (28 patients), and insulin glulisine (52 patients). After 3 to 6 months of treatment, significant weight gain was observed in the patients who had used insulin aspart and insulin glulisine (P = 0.008). However, in contrast to expectations, it was found that patients who had used insulin lispro experienced weight loss. Weight change in the patient group that used insulin lispro compared with weight change in the insulin glulisine group was found to be statistically significant (P = 0.034).

Conclusion: Our study showed that patients who used short-acting insulin analogues gained a little weight, patients who used insulin glulisine gained the most weight, and patients who used insulin lispro lost weight.

Key words: Type 2 diabetes mellitus, weight gain, insulin aspart, insulin lispro, insulin glulisine

1. Introduction

Diabetes mellitus, associated with defective insulin secretion and/or the effect of insulin, is a metabolic disease characterized by chronic hyperglycemia that results in a carbohydrate metabolism disorder. Chronic hyperglycemia may cause failure and dysfunction of various organs such as the eyes, kidneys, nerves, heart, and blood vessels (1). Insulin supplementation is the most effective agent for prevention of chronic hyperglycemia. Despite lifestyle changes and use of oral antidiabetic drugs, reduced percentage of the target glycolated hemoglobin (HbA1c) could not be obtained (2).

Insulin analogues have been developed to imitate the body's natural physiological secretion of insulin. Insulin aspart, insulin glulisine, and insulin lispro are rapid-acting insulin analogues. Insulin glargine and insulin detemir are long-acting insulin analogues and are used for provision of basal insulin levels (3,4). Intensive insulin therapy can reduce the risk of developing microvascular complications, or can delay the start of such complications by imitating baseline and postprandial insulin secretions. The most common side effects of insulin therapy are hypoglycemia, weight gain, insulin edema, allergy, antibody formation, and lipodystrophy (5). Studies reported that weight gain due to insulin was less with the use of analogue insulins than with human insulins (6–9). Despite these developments, weight gain due to insulin use continues to be a problem for many patients and doctors.

We could find no study in the literature about the effects of insulin analogues on weight gain in patients who use them. In our study, we aimed to investigate the effects of short-acting analogue insulins on weight, and to demonstrate the differences between them.

2. Materials and methods

Our study included 118 patients who used insulin glargine for 3–6 months with short-acting analogue insulins, i.e. insulin aspart (ins asp; 38 patients), insulin lispro (ins lis; 28 patients), and insulin glulisine (ins glu; 52 patients).

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Our study included patients who have used only intensive insulin therapy with metformin. Those who took other oral antidiabetics, other insulin derivatives, or different insulin combinations were excluded from the study because of the adverse effects on patients' weights. Patients' weights were recorded before and after 3 to 6 months of insulin use in order to determine the effects of insulins on weight gain. Each of the 3 groups were designed so that patients shared similar body mass index (BMI), sex, age, insulin dose, age of diabetes onset, and HbA1c levels. Patients were followed by the same dietician and used similar diet programs. In addition, patients' low density lipoprotein cholesterol (LDL-C) and triglyceride levels were examined. The study received ethics committee approval from the Bezmialem Vakıf University Faculty of Medicine.

HbA1c levels were measured by turbidimetric inhibition immunoassays. Triglyceride concentrations were measured by enzymatic assay (Boehringer Mannheim, Manheim, Germany). LDL-C was calculated with the Friedewald formula.

2.1. Statistical analysis

SPSS for Windows 13.0 was used for data analysis. Besides descriptive statistics (mean, median, and standard deviation), comparison of normally distributed parameters used one-way ANOVA, the post hoc Tukey test, and paired samples t-tests. For comparison of abnormally distributed parameters, Kruskal–Wallis, Mann–Whitney U, and Wilcoxon tests were used. The chi-square test was used to compare proportional data. Two-sided P-values of less than 0.05 were considered significant.

3. Results

This study consisted of 118 patients divided into 3 groups depending on whether they had used insulin glargine/ins asp (n = 38), insulin glargine/ins lis (n = 28), or insulin glargine/ins glu (n = 52). The 3 groups showed no statistically significant difference as to sex, age (P = 0.99), BMI, diabetes mellitus onset age, insulin glargine and short-acting insulin analogue doses, and baseline HbA1c levels (P = 0.76, P = 0.13, P = 0.57, P = 0.12, P = 0.21, and P = 0.18, respectively; Table 1).

Examination of weight changes in each of the 3 groups after 3–6 months of using short-acting insulin analogues showed that patients in the groups that used ins asp or ins glu gained weight. For the latter (ins glu), the gain was statistically significant (P = 0.008). Despite expectations, patients who used ins lis experienced weight loss. Comparison of weight changes between the ins lis and ins glu groups was statistically significant (P = 0.03).

Patients who had used analogue insulin were classified into 1 of 3 groups depending on whether they had lost weight (usually in the group that had used ins lis, P = 0.01), gained weight (mostly from the ins glu group), or had no weight change. Statistical significance was found in those who, in addition to insulin therapy, used metformin (1 pill of 1000 mg twice daily). Patients who used metformin were more often in the patient group that used ins glu (P = 0.02; Tables 2 and 3; Figures 1 and 2).

Patients in 3 groups were measured before and after a treatment period of 3 to 6 months with the following results for each group (Table 4):

1. Cholesterol levels: no statistical difference (P = 0.6, P = 0.4, P = 0.4, respectively).

Table 1. Comparison of age groups, BMI, and HbA1c.

	Ins asp (n = 38) Mean ± SD	Ins lis (n = 28) Mean ± SD	Ins glu (n = 52) Mean ± SD	P
Age	51.5 ± 10	52.3 ± 9.8	50.5 ± 10	0.76
BMI (kg/m²)	31.4 ± 6.6	28.2 ± 7.6	31.1	0.13
Diabetes age (years)	14.9 ± 7.7	13.8 ± 6.7	12.9 ± 6.7	0.57
Glargine (U)	27.7 ± 8.8	27.9 ± 7.4	32.7 ± 12.7	0.12
Short-acting insulin (U)	38.8 ± 14.2	46.9 ± 15.2	39.4 ± 18.6	0.21
HbA1c (%)	8.9 ± 1.8	9.0 ± 2.1	9.6 ± 1.8	0.18

Ins asp: insulin glargine + insulin aspart, ins lis: insulin glargine + insulin lispro, ins glu: insulin glargine + insulin glulisine, SD: standard deviation, BMI: body mass index, HbA1c: glycated hemoglobin, U: units.

Table 2. Comparison of weight gain of the groups.

	Ins asp (n = 38) Mean ± SD	Ins lis (n = 28) Mean ± SD	Ins glu (n = 52) Mean ± SD	P
Pretreatment weight (kg)	[3]80.7 ± 15.2	[£]76.3 ± 17.0	[â]80.8 ± 13.9	0.4
Posttreatment weight (kg)	[3]80.8 ± 15.0	[£]75.9 ± 16.8	[â]81.8 ± 14.4	0.24
Weight change (g)	39 ± 27	–428 ± 19*	1029 ± 27*	0.03
P	[3]0.93	[£]0.25	[â]0.008	

Ins asp: insulin glargine + insulin aspart, ins lis: insulin glargine + insulin lispro, ins glu: insulin glargine + insulin glulisine, SD: standard deviation.
*: Significant weight difference between ins lis and ins glu (P = 0.04).
3: P-value for ins asp group before and after treatment, £: P-value for ins lis group before and after treatment, â: P-value for ins glu group before and after treatment.

Table 3. Comparison of weight gain and additional therapy of the groups.

	Ins asp (n = 38)	Ins lis (n = 28)	Ins glu (n = 52)	P
Increased weight, n (%)	17 (44.7)	6 (21.4)	32 (61.5)	
No weight change, n (%)	9 (23.7)	8 (28.6)	9 (17.3)	0.01+
Decreased weight, n (%)	12 (31.6)	14 (50)	11 (21.2)	
Used metformin, n (%)	15 (39.5)	10 (35.7)	33 (63.5)	0.02*
Did not use metformin, n (%)	23 (60.5)	18 (64.3)	19 (36.5)	

Ins asp: insulin glargine + insulin aspart, ins lis: insulin glargine + insulin lispro, ins glu: insulin glargine + insulin glulisine.
+: Weight changes were statistically significant in the ins lis and ins glu groups (P = 0.002).
*: Weight changes were statistically significant between the ins lis and ins glu groups (P = 0.03).

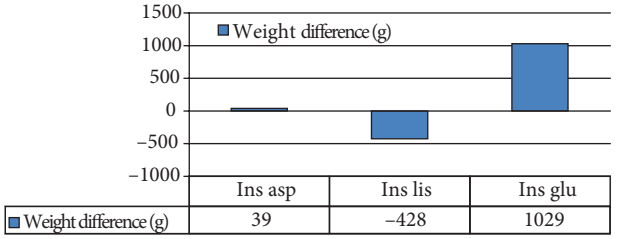

Figure 1. Weight changes according to groups: insulin glargine + insulin aspart (ins asp), insulin glargine + insulin lispro (ins lis), and insulin glargine + insulin glulisine (ins glu).

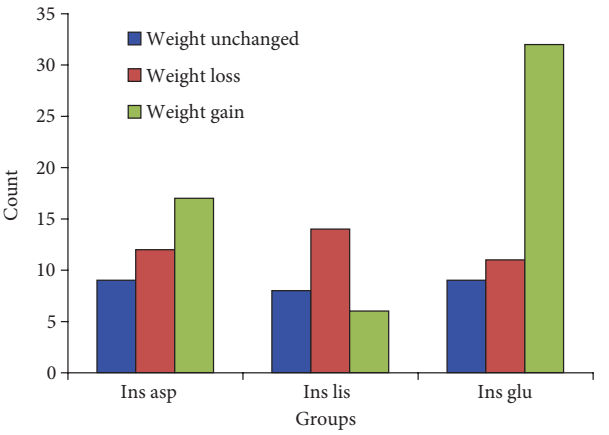

Figure 2. The distribution of those who lost weight, whose weight did not change, and whose weight increased, according to groups as defined in caption to Figure 1.

Table 4. The first and last measured LDL-C, triglycerides, and HbA1c levels.

	Ins asp (n = 38) Mean ± SD	Ins lis (n = 28) Mean ± SD	Ins glu (n = 52) Mean ± SD	P
LDL-C, first (mg/dL)	*116.6 ± 47.4	+122.3 ± 31	€111.6 ± 38	*0.6 +0.4 €0.4
LDL-C, last (mg/dL)	*112.9 ± 31	+116.6 ± 38	€106.7 ± 31	
Triglycerides, first (mg/dL)	*175.9 ± 10	+155.9 ± 10	€180 ± 17	*0.9 +0.2 €0.6
Triglycerides, last (mg/dL)	*197.2 ± 19	+177.3 ± 13	€184.1 ± 21	
HbA1c, first (%)	*8.9 ± 1.8	+9.0 ± 2.1	€9.6 ± 1.8	*0.8 +0.6 €0.7
HbA1c, last (%)	*9.0 ± 1.8	+8.9 ± 2.1	€9.5 ± 2	

Ins asp: insulin glargine + insulin aspart, ins lis: insulin glargine + insulin lispro, ins glu: insulin glargine + insulin glulisine, LDL-C, low-density lipoprotein cholesterol, HbA1c: glycated hemoglobin.
*: Shows P-value of before treatment and after treatment for LDL-C, triglycerides, and HbA1c of ins asp group.
+: Shows P-value of before treatment and after treatment for LDL-C, triglycerides, and HbA1c of ins lis group.
€: Shows P-value of before treatment and after treatment LDL cholesterol, triglycerides, and HbA1c of ins glu group.

2. Triglyceride levels: no statistical difference (P = 0.9, P = 0.2, P = 0.6, respectively).

3. HbA1c levels: no statistical difference (P = 0.8, P = 0.6, P = 0.7, respectively).

HbA1c levels measured at the beginning of treatment were similar in all 3 groups with no statistical difference among them (P = 0.18). After intensive treatment for 3 to 6 months, only 10.2% of the patients reached the targeted HbA1c level (<7%). There was no significant difference among the 3 groups who used insulin in achieving the target HbA1c level (P = 0.37).

4. Discussion

Short-acting analogue insulins imitate physiological insulin secretion but have the negative side effect of causing weight gain. The aim of our study was to determine the potential weight gain of short-acting analogue insulins in patients who use them and to determine possible differences between the analogue insulins. In addition, we aimed to determine the effects of analogue insulins on LDL-C and triglycerides. In order to reduce unintended external effects that could alter the results, our study included patients with similar demographic characteristics and HbA1c levels. To determine the effect of short-acting insulin analogues, our study included only patients who had used insulin glargine as long-acting insulin.

Analysis of pre- to posttreatment weight change of all 3 groups showed that the patients who used ins asp and ins glu gained weight (up to 6 kg), whereas patients who used ins lis lost weight. This result was statistically significant. Patients who had used ins glu gained a statistically significant amount of weight. For this reason, we divided patients into 3 groups: those who lost weight, those who gained weight, and those whose weight did not change. Even in this situation, the results remained unchanged and statistically significant. The majority of the weight loss patients were in the group that had used ins lis. The majority of the weight gain patients were in the group that had used ins glu. Evaluating other drugs that could possibly affect the results, we found that this was only the case among metformin users, most of whom were in the group that had used ins glu. This was statistically significant. Since metformin is an oral antidiabetic that may help in weight loss, one may reasonably assume that ins glu used alone might lead to weight gain.

We found no studies related to any effect on weight gain of our 3 short-acting insulin analogues. Some studies investigated weight gain of users of other insulin groups, such as neutral protamine Hagedorn (NPH) insulin, insulin detemir, and insulin glargine (6–10). Temizel et al., comparing analogue insulin mixtures at 6 and 12 months in their study, found a 1.41 ± 2.7 kg and 2.08 ± 3.7 kg weight

gain in patients using ins lis and a 1.5 ± 3.0 kg and 2.29 ± 3.8 kg weight gain in patients using ins asp, respectively, but these results did not have statistical significance (11). Similarly, in our study, we found no difference between ins asp and ins lis, except that ins lis had less effect on weight gain. Fritsche et al. compared insulin glargine and ins glu (basal-bolus therapy) and insulin premix (twice daily) and found that by week 52, patients using basal-bolus therapy gained 3.6 kg and patients using insulin premix gained 4.5 kg. They also found that HbA1c levels of the patients using basal-bolus therapy decreased 1.31%, and HbA1c levels of the patients using insulin premix decreased 0.8% (P = 0.0001) (12). Even though the duration of our study was shorter, their insulin glargine and ins glu results are relatively similar to ours. In that study, although they used intensive treatment for 52 weeks, patients did not achieve target HbA1c levels.

In our study, when we considered the causes for these differences, we thought that short-acting insulin analogues had similar effects and features, but essentially they are different molecules. Therefore, although the starting time of effect, peak time, and duration of the action of ins asp and ins lis are similar, ins glu has a shorter duration of action and so its peak time is faster (13). Periods of hypoglycemia lengthen as a result of more rapidly declining plasma glucose levels. Depending on this rapid peak and more short-term effect, the feeling of hunger increases and patients eat more, which leads to adverse effects on weight. In addition, although patients received intensive insulin therapy, patients could not achieve the expected HbA1c levels, but this was not a factor that could have affected weight gain because HbA1c levels were similar in all 3 groups.

In conclusion, our study showed that patients who used short-acting insulin analogues gained a little weight, patients who used ins glu gained the most weight, and patients who used ins lis lost weight. The effects of short-acting insulin analogues on LDL-C and triglyceride levels were neutral. As a result, when selecting intensive insulin therapy for a patient, weight gain should be taken into account, and treatment options should be determined by taking into consideration the patient's condition.

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