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LIPODYSTROPHY FREQUENCY ACCORDING TO INSULIN TREATMENT REGIMEN IN TYPE 2 DIABETIC PATIENTS: IS INSULIN INJECTION FREQUENCY MATTERS IN ANALOG INSULIN ERA?

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Abstract

Objectives. We aimed to determine lipodystrophy frequency according to insulin treatment regimen and insulin injection frequency in type 2 diabetic patients.

Methods. A total of 345 type 2 diabetic patients under insulin treatment for at least one year were included in this cross-sectional study. Patients were examined for presence of lipodystrophy, insulin injection frequency and dosage. Lipodystrophy was evaluated with visual inspection and palpation of all injection sites. Patients were evaluated into three categories according to daily insulin dose requirement: Group 1= Standard-dose insulin users 0.6 U/kg/day; Group 2= Medium-dose insulin users 0.61-1.9 U/kg/day, Group 3= High-dose insulin users ≥2 U/kg/day.

Results. Lipodystrophy was seen in 28% of the patients. Lipodystrophy was significantly higher in group 3. There was no significant difference between the groups in terms of lipodystrophy size. Duration of insulin treatment, daily total insulin dose, daily insulin dose per weight and number of daily insulin injections were significantly higher in the group with lipodystrophy. Daily injection number of long-acting, rapidly-acting analog and total insulin injections were significantly higher in group 3 than group 1 and 2. Number of daily insulin injections and lipodystrophy frequency were significantly higher in basal-bolus insulin user group. Multivariate analysis showed that insulin injection frequency is the independent risk factor for lipodystrophy.

Conclusion. Lipodystrophy is still a clinical problem in patients with high-dose insulin requirement and frequent insulin injections. Reducing daily insulin requirement and daily number of injections should be given priority in the management of patients to prevent the development of lipodystrophy.

Keywords: Diabetes Mellitus Type 2, insulin, lipodystrophy, lipohypertrophy, lipoatrophy.

INTRODUCTION

Diabetes mellitus is a progressive disease by nature, and as a result, many patients with Type 2 diabetes (T2DM) eventually need insulin therapy and benefit from it (1). Insulin therapy is the preferred method of treatment where oral antidiabetic drugs are not sufficient (1).

Guidelines suggest basal insulin for initiation in insulin therapy in insulin naïve patients and basal-plus, basal-bolus and premixed insulin for intensification of the insulin therapy. Thus, in most type 2 diabetic patients, the insulin dose and the number of injections are increased in the later stage (1,2).

Insulin therapy is associated with acute, general and local complications such as hypoglycemia, insulin allergy and lipodystrophy in the clinical practice. Local complications are reported despite the use of new generation analog insulins (3).

Lipodystrophy is frequently reported in patients using subcutaneous insulin injection and presents as lipohypertrophy (LH) or lipoatrophy (LA) (4,5). LH is the area of thickened subcutaneous fat tissue confined to insulin injection sites in the form of painless induration, swelling, and nodules lacking an external capsule and steadily growing over time with repeated injections (6). Strong growth-promoting properties of insulin, repetitive trauma caused by injecting into the same place without rotation and re-injection without changing the needle tip are considered to be the causes of LH (4,5).

Lipoatrophy is the loss of subcutaneous fat tissue by palpation and visible cutaneous depression at the injection site. Since LA is more common in type 1 diabetes (T1D) patients and women, its etiology is

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thought to be immunological. In addition, there is a lipolytic reaction in LA, possibly caused by components of some insulin preparations, but the prevalence of LA decreases as the insulins are purified (7).

Since the site of LH lesion is painless, it is common among patients to inject there. However, the absorption of insulin injected into this area is reduced and variable. This can lead to increased insulin needs and also cause high glycemic variability (8). From this point of view, patients should be examined for LH in the presence of unexplained hypoglycemia and glycemic variability (10).

The factors affecting the development of LH have been cited as gender, body mass index (BMI), duration of insulin treatment, number of daily injections, injection sites, rotation of injection sites, usage of pens instead of syringes, size of the needle and frequency of needle switch (9-18). While BMI, insulin treatment duration and high HbA1c have been shown to be risk factors for the development of LH in some studies, they have not been shown in other studies.

In this study, we aimed to examine LD frequency and its relationship between different insulin treatment regimens and insulin dose requirement in type 2 diabetic patients.

MATERIALS AND METHODS

Patient selection

This cross-sectional and retrospective study conducted with 345 consecutive type 2 diabetic patients who were evaluated between May 2018- June 2019 in Marmara University Pendik Training and Research Hospital Endocrinology and Metabolism outpatient clinic.

Patients under age of 18 years and over 90 years, patients with type 1 diabetes mellitus, women with gestational diabetes, insulin treatment usage less than one-year, acute hyperglycemia who did not use insulin ordinarily and hospitalized patients exluded from the study.

Clinical evaluation

Demographic and laboratory data were recorded from patients' files. The parameters evaluated in study were: age; gender; BMI (height and weight were measured, BMI was calculated by dividing the weight in kilograms by the square of the height in meters (kg/m^2)); duration of diabetes; comorbidities such as hypertension (HT), hyperlipidemia (HL), coronary artery disease (CAD), oral antidiabetic drugs (metformin, inhibitors of dipeptidyl peptidase 4 (DPP4i), sodium-glucose co-transporter-2 inhibitors (SGLT2i), glucagon-like peptide 1 receptor agonists (GLP-1a), glitazone); insulin treatment regimens (basal, basal-plus, basal-bolus, premixed); daily total, long and rapidly acting insulin doses and daily insulin dose per weight; daily number of injections of rapidly-acting, long-acting and total insulin injection and needle lenght were recorded.

Study group was divided into three categories according to the insulin dose they use kilogram per day: Group 1= Standard dose insulin users 0.6 U/kg per day; Group 2= Medium dose insulin users 0.61-1.9 U/kg per day, Group 3= High dose insulin users ≥2 U/kg.

Lipodystrophy evaluation

Patients underwent a structured physical examination visual inspection and palpation of all injection sites. The patients were examined based on Ji *et al.* method as previously explained in the literature (19). Examinations were made in warm rooms (to avoid shivering) with oblique lighting to aid visual inspection, and examiners' hands were washed and warmed. For abdominal examinations, patients were in supine position on the examination table with knees drawn up to relax abdominal musculature. Light-to-moderate pressure with small sweeps of the finger tips was used to expose LH lesions. When found, lesion dimensions (longest diameter and perpendicular length) were marked with a pen, measured and recorded. The number of lesions in an area was noted, but dimensions only recorded for the largest lesion. For the thigh, patients were examined sitting with knees bent and feet on the floor. The arm and buttock were similarly evaluated (patient standing for the latter), if the patient injected at such sites. Obtained data was evaluated according to presence (LD+) and absence (LD-) of lipodystrophy.

The study was approved by the Marmara University School of Medicine's local ethics committee (09.2018.399) and was conducted following the ethical principles stated in the Declaration of Helsinki.

Biochemical Parameters

Biochemical results measured in the last 3 months were recorded from the patients' files. Fasting plasma glucose levels (FPG) were measured using an enzymatic UV test (hexokinase method). HBA1c was analyzed with high-performance liquid chromatography in Premier Hb9210 (Trinity Biotech, USA).

Statistical analysis

All the statistical analyses were made using SPSS (Statistical Package for the Social Sciences) version 20.0. Descriptive data was stated as frequencies (%) for categorical data, means, and standard deviations (SD) for continuous data with a normal distribution. A comparison of two groups was made with Student's t-test or Mann-Whitney U test appropriately. Three group comparisons were made Kruskal wallis ANOVA test. We used Spearman's correlations for nonparametric values and two-tailed probability values to predict the strength of the relationship between variables. Linear multiple regression analyses with a stepwise procedure were performed to define the factors associated with lipodystrophy. Age, BMI, daily insulin dose per weight, duration of insulin treatment, dose of daily rapidly-acting and long-acting analog insulin, total daily dose of insulin, total daily number of injections, HbA1c values were included as independent risk factors.

The statistical significance level was accepted as $p<0.05$. All of the results were stated as mean±SD.

RESULTS

In this study, LD was detected in 98 patients (28,4%), LH was detected in 93 patients (27%) and LA was found in 5 patients (1.4%).

Clinical and laboratory characteristics of type 2 diabetic patients according to presence of lipodystrophy were shown in Table 1. The group with lipodystrophy was younger than the group without LD ($p<0.0001$). There was no significant difference between LD+ and LD- group according to FPG, HbA1c, gender, duration of diabetes, BMI and oral antidiabetic drug using frequency.

Duration of insulin treatment($p=0.031$), daily insulin dose per weight ($p=0.0058$) and total insulin dose in a day ($p=0.0063$) were significantly higher in

Table 1. Clinical and laboratory characteristics of type 2 diabetic patients according to presence of lipodystrophy

	Lipodystrophy (+) (n=98)	Lipodystrophy (-) (n=247)	p
Age (years)	57±9.6	57±11	**<0.0001**
Gender (Male/Female)	60/ 38	148/ 99	0.975
Duration of diabetes (years)	16±8.3	14±7.3	0.16
BMI (kg/m^2)	37±9.1	37±8.3	0.72
HT (yes/no)	76 (77%)	164/83	0.057
HL (yes/no)	82 (84%)	195/52	0.39
CAD (yes/no)	36 (37%)	167 (67%)	**<0.0001**
FPG (mg/dL)	177±73	191±9.3	0.2
HbA1c (%)	8.5±1.7	9.3±7.8	0.23
Oral antidiabetic agents			
Metformin	66 (67%)	159 (64%)	0.69
DPP4i	41 (42%)	110 (44%)	0.73
SGLT2i	12 (18%)	32 (13%)	0.85
GLP1a	3 (%3)	15 (6%)	-
Glitazone	1 (%1)	-	-
Daily insulin dose per weight (IU/kg)	1.3±0.98	0.99±0.59	**0.0058**
Duration of insulin treatment (years)	10±6.2	8.4±5.5	**0.031**
Total insulin dose (IU/day)	119±96	95±61	**0.0063**
Dose of rapidly-acting analog insulin (IU/day)	66±60	53±38	0.081
Dose of long-acting analog insulin (IU/day)	58±41	49±29	0.083
Number of insulin injections per day	3.7±0.99	3.2±1.3	**0.0004**
Needle lenght (mm)			
-8	7 (7.1%)	24 (9.7%)	0.38
-6	20 (20.4%)	44 (17.8%)	
-5	18 (18.4%)	28 (11.3%)	
-4	53 (54.1%)	151 (61.2%)	
Size of lipodystrophy (mm)	14.5 (2-20)	-	
Single/multiple lipodystrophy (n)	45/53	-	
Site of lipodystrophy (n)			
-Abdomen	53 (45%)	-	
-Arms	42 (36%)	-	
-Thighs	20 (17%)	-	
-Buttocks	2 (2%)	-	

the LD+ group compared to the LD– group.

There was no significant difference between LD+ and LD- group in terms of daily insulin requirement for rapidly-acting analog and long-acting analog insulin. The number of insulin injections was significantly higher in LD+ group than LD- group (p=0.0004). Injection needle length was similar both LD+ and LD- group and most of the patients were using 4 mm needle for insulin injection.

Clinical and laboratory parameters according to daily insulin dose requirement were shown in Table 2. The mean age of patients with standard dose insulin requirement (≤0.6 U/kg) (group 1) was significantly higher than patients with daily requirement 0.61-1.9 U/kg (group 2) and patients with daily requirement ≥2 U/kg (group 3) (p=0.002). There was BMI was significantly lower in group 1 compared to group 2 and 3 (p=0.0008), although groups were similar in terms of gender and duration of diabetes.

Duration of insulin treatment was significantly lower in high dose insulin required patients (group 3) compared to group 2 and 1 (p<0.0001). FPG and HbA1c levels were higher in group 3 compared to group 1 (p<0.0001) and group 2 (p<0.0001). Daily dose of long-acting, rapidly-acting analog insulin and total daily insulin dose were found to be significantly higher in group 3 compared to the other groups. The daily injection number of long-acting and rapidly-acting insulin and total daily number of insulin injections were also significantly higher in group 3 than the other groups (p<0.0001, p=0.0025, p<0.0001, respectively). The lipodystrophy frequency was statistically significantly higher in group 3 compared to the other groups (p=0.001) and there was no significant difference between the groups in terms of lipodystrophy size.

Clinical and lipodystrophy evaluation according to insulin treatment regimen was shown in Table 3. The number of insulin injections and lipodystrophy frequency were significantly higher in basal-bolus insulin user group compared to pre-mixed insulin user and basal insulin user groups (p<0.0001, p=0.022) and there was no difference between the groups in terms of lipodystrophy size. Total daily insulin dose and daily insulin dose per weight were found to be significantly higher in basal-bolus insulin user group than the other groups (p=0.0004, p<0.0001, p<0.0001, respectively). The groups were similar according to duration of

Table 2. Clinical and laboratory parameters according to daily insulin dose requirement

	Group 3 (high dose insulin: ≥2 U/kg) (n=32)	Group 2 (medium dose insulin: 0.61-1.9 U/kg) (n=228)	Group 1 (standard dose insulin: ≤0.6 U/kg) (n=85)	p
Age (years)	52±9.2	57±11	61±9.8	**0.002**
Gender (Male/Female)	22/10	142/86	44/41	0.231
Duration of diabetes (years)	14±7.0	15±7.9	13±7.0	0.051
BMI (kg/m^2)	38±8.7	38±8.2	34±8.7	**0.0008**
Daily insulin dose per weight (IU/kg)	2.6±1.0	1.1±0.36	0.39±0.14	**<0.0001**
FPG (mg/dL)	275±160	185±75	159±56	**<0.0001**
HbA1c	10±2.6	9.3±8.1	8.1±1.6	**<0.0001**
Duration of insulin treatment (years)	9.9±5.5	9.7±5.8	6.3±5.0	**<0.0001**
Dose of rapidly-acting analog insulin (IU/day)	135±7.1	56±29	15±8.2	**<0.0001**
Dose of long-acting analog insulin (IU/day)	112±8.4	53±23	24±11	**<0.0001**
Total insulin dose (IU/day)	247±108	107±42	34±15	**<0.0001**
The injection number of rapidly-acting analog insulin (n/day)	3.0±0.0	3.0±0.19	2.7±0.66	**0.0025**
The injection number of long-acting analog insulin (n/day)	1.6±0.5	1.2±0.4	1.2±0.39	**<0.0001**
The total number of insulin injections (n/day)	4.3±0.79	3.6±0.97	2.1±1.1	**<0.0001**
Size of lipodystrophy (mm)	13.50 (5-50)	15 (3-120)	11 (2-90)	0.760
The presence of lipodystrophy (n)	12 (37.5%)	80 (35.1%)	14 (16.5%)	**0.001**
Single/multiple lipodystrophy (n/n)	5/7	30/50	10/4	
Site of lipodystrophy (n)				
-Abdomen	6 (%43)	40 (%48)	7 (%47)	
-Arms	7 (%50)	28 (%34)	3 (%20)	
-Thighs	1 (%7)	13 (%16)	5 (%33)	
-Buttocks	-	2 (%2)	-	

diabetes. BMI and FPG values were significantly higher in the basal-bolus insulin user group compared to the other groups (p=0.0174, p=0.049). HbA1c levels and duration of insulin treatment were significantly higher in pre-mixed insulin user group than basal and basal-bolus insulin user groups (p=0.0027, p=0.0004, respectively).

When lipodystrophy was taken as an independent risk in multivariate analysis and age, BMI, daily insulin dose per weight, duration of insulin treatment, dose of rapidly-acting, long-acting analog insulin and total dose of daily insulin, total number of daily injections, HbA1c values were evaluated as variables, a statistically significant relationship between the total number of injections and lipodystrophy was revealed (r2=6.08%, p=0.034).

DISCUSSION

In this study, we found the frequency of lipodystrophy to be 28.4% in our type 2 diabetic patient group. For the presence of LD, high-dose insulin requirement and the number of insulin injections were found independently associated.

Frequency of LD in our type 2 diabetic patient group was in concordance with the recent literature which was reported in a wide range. The prevalence of LH in Jordan, Spain, Germany, China and the United Kingdom were 37.3%, 3.6%, 53.1%, 56%, and 28%, respectively (2,13,19-21). Considering this wide range of rates in the literature, it was found to be low compared to the literature.

In a study includes 436 T2DM patients in Turkey, the prevalence of LD was reported to be 43.8% (23). Dagdelen S. *et al.* made a large-scale study later, which involving 1376 patients with LD detection rate was found 27.4% (24). Our findings regarding the presence of LD are consistent with the current literature.

In a recent systematic review and meta-analysis Deng and colleagues reported the prevalence of LH as 38% and they found that LD frequency in Asian countries was higher than that of European countries (22). They stated that this situation might have something to do with social and cultural factors, however, most of the studies conducted in Asia were published later, so recent publications may be associated with the increased prevalence of LH among patients with diabetes mellitus. In our country, which is located in the middle of Asia and Europe, the LD rate was found to be lower based on this review.

LD in patients with diabetes was found to be more frequent in abdominal region in studies performed in European countries (21,25,26). In our study, LD was detected mostly in abdomen (45%) and arm (36%). The reason why diabetics prefer the abdomen and arm for insulin injection is probably the ease with which the clothes can be removed.

Lipodystrophy is more frequent in patients who administer insulin injections four times per day. The studies conducted in the literature and the results of this study also emphasize that the incidence of lipohypertrophy increases in parallel with the increase in the number of injections per day (21,29).

Insulin itself shows a strong growth hormone effect. In the study of Blanco and colleagues, the incidence of lipohypertrophy was found to be less in patients receiving only basal insulin therapy than those receiving basal+bolus insulin therapy (21). The results of our study are also consistent with these findings. It is thought that as the number of daily injections administered to the injection site increases, the frequency of lipohypertrophy in the injection site increase because the region is exposed to much more insulin and thus trauma. Another finding of this study,

Table 3. Clinical and lipodystrophy evaluation according to insulin treatment regimen

	Basal-bolus insulin (n=208)	Premixed insulin (n=100)	Basal insulin (n=37)	p
Age (years)	55±10.4	60±11	57±8.7	**0.003**
Duration of diabetes (years)	15±7.4	15±7.4	13±7.2	0.42
BMI (kg/m^2)	37±8.6	35±7.5	34±9.0	**0.0174**
FPG (mg/dL)	193±82.1	184±104.0	155±59.8	**0.049**
HbA1c (%)	9±2.0	9.6±12.0	8±1.3	**0.0027**
Duration of insulin treatment (years)	9±5.8	9.2±5.6	5.4±4.0	**0.0004**
Daily insulin dose per weight (IU/kg)	1.3±0.7	0.8±0.47	0.39±0.2	**<0.0001**
Total dose of insulin (U/day)	127±78	75±43.6	33±19.7	**<0.0001**
The total number of insulin injections (n/day)	4 (1-5)	2 (1-3)	1 (1-2)	**<0.0001**
The presence of lipodystrophy (n)	70 (33.6%)	20 (20%)	7 (18.9%)	**0.022**
Size of lipodystrophy (mm)	25±25.8	22±17.0	24±24.6	0.919

namely lipohypertrophy is less frequent in patients who only administer basal insulin, supports this assertion. Because the patients who only use basal insulin inject once a day but those who receive basal+bolus therapy administer four or more injections per day. According to the data in our study, the increase in the number of insulin injections was found to be an independent risk factor for the development of lipodystrophy.

Studies in the literature, it was found that the incidence of LD increases in patients with A1c level ≥7% (19,27,28). In our study A1c level is about 8.5% but there was no significant difference between the group without lipodystrophy and those with lipodystrophy. It may be because the group with LD+ has been diabetic for a longer time and has been using insulin treatment for a longer period of time. In addition, because the LD+ group was younger, they were use higher doses of insulin and more insulin injection numbers to reach their HbA1c target.

In the literature, the frequency of lipohypertrophy was higher in obese patients (19,28). Although BMIs of the group with LD and the group without LD were similar in our study, it was observed that BMI increased as the number of daily injections increased.

Clinical guidelines of Tandon *et al.* reported that 4 mm needle provides better glycemic control and reduces the risk of intramuscular injection and thus less pain during the injection (9). We think that one of the reasons for the lower frequency of LD in our study compared to other studies was that the patients in our study preferred shorter needles (4 mm) (54.1%). And we think that regular patient education by trained nurses makes an important contribution to the determination of low LD rate.

The limitations of our study; the gold standard of LD evaluation, ultrasonography was not used in patients in our study, due to study design as a retrospective and cross-sectional study, and some patients' data on lipodystrophy (injection rotation frequency, needle reuse, etc.) could not be obtained and therefore could not be included in the analysis.

In conclusion, it is important that patient education and lipodystrophy examination become routine to reduce complications in the evaluation of diabetic patients using insulin. In addition, the number of injections is the most important independent risk factor, and reducing the number of injections should be prioritized in the management of type 2 diabetic patients.

Conflict of interest

The authors declare that they have no conflict of interest.

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