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Prevalence of Lipohypertrophy and Lipoatrophy in Individuals with Type 2 Diabetes and Determination of Associated Risk Factors

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Abstract

Background: This study aimed to determine the prevalence of lipohypertrophy and lipoatrophy and their associated risk factors in individuals with type 2 diabetes taking insulin.

Methods: This descriptive and cross-sectional study used the STROBE checklist. In January 2022 to April 2022, 271 individuals with type 2 diabetes were studied. The presence of lipoatrophy and lipohypertrophy was evaluated with inspection and palpation, and the sociodemographic and clinical characteristics of the patients were obtained using a questionnaire. Data were collected in face-to-face interviews.

Results: Lipoatrophy and lipohypertrophy prevalence was 4.8% and 19.2%, respectively. Lipoatrophy was more common in patients who did not perform regular intra-regional rotation, and lipohypertrophy in those aged ≤60 years, women, those using insulin at a dose of >50 IU, those administering four injections per day, those using prandial and basal insulin, and those who did not perform regular systematic and intra-regional rotation ($p < 0.05$).

Conclusions: Lipoatrophy and lipohypertrophy are common in patients with type 2 diabetes mellitus taking insulin and may develop due to some modifiable risk factors.

Keywords: diabetes mellitus, insulin, lipodystrophy, lipohypertrophy, risk factors

INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disorder with a wide clinical spectrum that results from relative or absolute insulin deficiency or resistance against the effects of insulin in peripheral tissues and is characterized by hyperglycemia causing multisystem involvement.[1] Lipodystrophies are critical complications of insulin therapy, which is a treatment option in the management of type 2 diabetes. Lipodystrophies, such as lipoatrophy and lipohypertrophy, are skin complications from insulin administration at the injection site.[2] Lipodystrophy is more common in type 1 diabetes; however, its frequency is considerably high in type 2 diabetes.[3,4] In a study conducted in Spain, 49.1% of individuals with diabetes and lipohypertrophy and 5.9%–6.5% of those with diabetes and without LH had severe unknown hypoglycemia.[3,4] Detecting lipodystrophic lesions is challenging for individuals with diabetes and healthcare professionals, and health professionals may not be sufficiently aware of this condition.[5,6]

Lipohypertrophy is the swelling and firming of the insulin injection site due to increased mass of fatty tissue in that region. The prevalence of lipohypertrophy in Turkey is 43.8%–61.8%.[7,8] In contrast, lipoatrophy is defined as a tissue depression caused by fat atrophy at the insulin injection site. In our country, the prevalence of lipoatrophy is lower than that of lipohypertrophy (5.6%).[7] Most patients prefer a lipohypertrophic region for insulin injection owing to problems in insulin absorption and decreased sense of pain. However, this leads to an increase in insulin consumption and thus in costs. Furthermore, insulin absorption in a lipodystrophic region is inconsistent, which causes difficulties in maintaining the ideal blood glucose level.[7–12] Diabetic patients with lipodystrophy using high amounts of insulin and failing to manage the disease suffer from various chronic complications, such as cardiovascular disorders, amputation, retinal diseases, renal diseases, and body image disturbance, and an increased economic burden.[12–16] Although preventing lipodystrophy is the primary objective of healthcare professionals, educational and counseling services should be developed. Therefore, this study aimed to determine the prevalence of lipohypertrophy and lipoatrophy and its associated risk factors in individuals with type 2 diabetes using insulin.

METHODS

Written permissions were granted by the Ankara Provincial Health Directorate (no. E-90739940-799; dated January 3, 2022), from the TÜEK unit of Ankara City

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Hospital where the study was conducted (no. 34, dated December 29, 2021), and Çankırı Karatekin University Ethics Committee (ethics committee no. 23, dated November 9, 2021). Written and verbal consent was obtained from the participants. The Declaration of Helsinki principles were followed throughout the study.

This descriptive and cross-sectional study used the STROBE checklist. Data were collected from 271 individuals with type 2 diabetes using insulin treated at the Endocrinology and Metabolic Diseases and Internal Medicine outpatient clinics of a state hospital in Ankara City Center between January 2022 and April 2022. Individuals who met the inclusion criteria were selected using non-probability random sampling. In a study by Buyruk *et al*. in 2019, lipohypertrophy prevalence was found to be 61.8%, and the study result was utilized to determine the sample size. When most of the study data were obtained, lipohypertrophy prevalence was calculated, the sample was reevaluated within the study itself, and the number of samples was determined to be 271.

The study sample included adults who had been administering the same insulin type for 6 months or longer, who had been self-administering pen insulin at least once daily, and who had been previously untreated for lipohypertrophy and lipoatrophy. Patients who could not use any injection site for various reasons such as an amputated extremity, burns, fractures, or incisions; those who were using an insulin pump; those who were taking treatments modifying lipodystrophy, such as octreotide, corticosteroid, or antiretroviral therapy; those who were using repeated subcutaneous drugs other than insulin, which were administered to the same region; and those who had visual, auditory, or speech disturbances that were so severe to affect communication were excluded, as well as a patient with simultaneous lipoatrophy and lipohypertrophy because she would be classified in both categories.

Study data were collected in three stages. First, the eligible individuals underwent physical examination for lipodystrophy and anthropometric measurements. Then, a questionnaire, which was prepared by all researchers in light of a literature review and consisted of 18 items related to sociodemographic and clinical patient characteristics, was filled.[3,4,8,17–19] Last, the patients' glycosylated hemoglobin (HbA1c) values for the last 6 months were obtained from the hospital information management system. According to the ADA criteria, glycemic control was controlled if the HbA1c level was ≤7% and uncontrolled if >7%.[20]

Study data were obtained by the first researcher through face-to-face interviews. Before the start of the study, the first researcher was trained by diabetes training nurses on the diagnosis of lipoatrophy and lipohypertrophy, and the researcher observed and practiced for a day. All data were collected by the first researcher. The presence of lipoatrophy and lipohypertrophy at all injection sites was evaluated by inspection and palpation at daytime, with the patient in a lying or sitting position. During the physical examination, the injection sites were first assessed by the investigator by observing them directly and tangentially, then using a light palpation technique including fingertip movements, and then by performing a compression maneuver in the suspected lipohypertrophy area. In the literature, the degree of lipohypertrophy was graded as follows: grade 1, lipohypertrophy without visible skin lesion but increased palpable density of subcutaneous tissue, and grade 2, dense fatty tissue thickening of firm consistency.[6,21] No grading has been reported for lipoatrophy.

Data were analyzed using the Statistical Package for Social Sciences 25.0 program and descriptive statistical methods (i.e., number, percentage, and prevalence). Chi-square analysis was employed to analyze risk factors affecting lipohypertrophy and lipoatrophy prevalence; when the variables did not meet the assumptions of normal distribution, Fisher's exact test was used. $P < 0.05$ indicated statistical significance. A regression analysis could not be conducted because no significant model could be established.

RESULTS

Among the individuals with type 2 diabetes who participated in the research, 35.1% (N = 95) were aged 61–70 years, 62% (N = 168) were women, and 46.5% (N = 126) were primary school graduates. The prevalence of lipoatrophy and lipohypertrophy was 4.8% (N = 13) and 19.2% (N = 52), respectively. The lesion was located in the abdominal region in 51.9% (N = 27) of the patients with lipohypertrophy and 84.6% (N = 11) of those with lipoatrophy. Among patients with lipohypertrophy, 12.5% had grade 1 lesions, and 6.6% had grade 2 lesions (Table 1).

Thirty-five percent of the studied patients with diabetes were aged 61–70 years, 62% were females, 43.2% had diabetes for 16 years or longer, 31.7% had been using insulin for 0–5 years, 56.1% were using insulin at a daily dose of ≤50 IU (international units), 47.6% applied four insulin injections/day, and 56.5% were on prandial and basal insulin therapy. Among the participants, 76.8% used the abdominal region for insulin injection, 41.7% used at least two regions, 38.4% used a different region for each injection, and 59% did not perform regular intra-regional rotation. Moreover, 41.3% of the patients were obese, and 81.5% had an HbA1c level >7%.

Lipoatrophy was more common in those who did not perform regular intra-regional rotation and lipohypertrophy in patients aged ≤60 years, women, those using

TABLE 1. Prevalence of lipoatrophy and lipohypertrophy

Variable	N	%
Lipoatrophy		
Present	13	4.8
Absent	258	9.2
Lipoatrophy region		
Arm	1	7.7
Abdomen	11	84.6
Thigh	1	7.7
Lipohypertrophy		
Present	52	19.2
Absent	219	80.8
Lipohypertrophy grade		
1	34	12.6
2	18	6.6
Lipohypertrophy region		
Arm	15	28.8
Abdomen	27	51.9
Thigh	10	19.2

insulin at a dose >50 IU/day, those using four injections or more daily, those using prandial and basal insulin, and those who did not perform regular systematic and intra-abdominal rotation ($p < 0.05$) (Table 2).

DISCUSSION

In the present study, lipohypertrophy and lipoatrophy prevalence were 19.2% and 4.8%, respectively. Previous studies have reported the prevalence of lipohypertrophy to be 35.2% in China, 39.7% in Saudi Arabia, 48.8% in Turkey, 54.9% in Egypt, 64.4% in Spain, and 68% in India.[4,13,17,19,22,23] A study conducted in Turkey showed a prevalence of lipoatrophy of 5.6%, whereas a study from Thailand found a prevalence of 1%.[6,7] A decrease in the prevalence of lipohypertrophy has been noted in the last decade.[8] The prevalence of lipodystrophy was lower in our study than in previous reports. While this finding is pleasing, it is believed to result from technological advances in insulin therapy, an increased number of diabetes experts, and easier patient access to information.[24]

TABLE 2. Correlation between the presence of lipoatrophy and lipohypertrophy based on sociodemographic data

Variables/Test Value	N (%)	Lipoatrophy			Lipohypertrophy		
		Present N (%)	Absent N (%)	*p*	Present N (%)	Absent N (%)	*p*
Age							
≤60 years	85 (31.4)	3 (23.1)	82 (31.8)		27 (51.9)	58 (26.5)	
61–70	95 (35.0)	7 (53.8)	88 (34.1)	0.346	12 (23.1)	83 (37.9)	0.002*
≥71 years	91 (33.6)	3 (23.1)	88 (34.1)		13 (25.0)	78 (35.6)	
Sex							
Female	168 (62.0)	8 (61.5)	155 (61.5)	0.972	42 (80.8)	126 (57.5)	0.002*
Male	103 (38.0)	5 (38.5)	98 (38.5)		10 (19.2)	93 (42.5)	
Body mass index (BMI)							
Below normal	8 (3.0)	0 (0.0)	8 (3.0)		2 (3.8)	6 (2.7)	
Normal	61 (22.5)	2 (15.5)	59 (22.9)	0.409	7 (13.6)	54 (24.7)	0.150
Overweight	90 (33.2)	6 (46.2)	84 (32.6)		15 (28.8)	75 (34.2)	
Obese	112 (41.3)	5 (38.6)	107 (41.5)		28 (53.8)	84 (38.4)	
Duration of diabetes							
0–5 years	36 (13.3)	1 (7.6)	35 (13.6)		8 (15.4)	28 (12.8)	
6–10 years	57 (21.0)	2 (15.5)	35 (21.3)	0.828	12 (23.1)	45 (20.5)	0.883
11–15 years	61 (22.5)	3 (23.1)	58 (22.5)		10 (19.2)	51 (23.3)	
≥16 years	117 (43.2)	7 (53.8)	110 (42.6)		22 (42.3)	95 (43.4)	
HbA1c level							
≤7%	49 (18.5)	1 (7.6)	48 (19.0)	0.304	10 (19.2)	39 (18.3)	0.878
>7 %	216 (81.5)	12 (92.4)	204 (81.0)		42 (80.8)	174 (81.7)	
Duration of insulin therapy							
0–5 years	86 (31.7)	4 (30.7)	82 (31.8)		19 (36.5)	67 (30.6)	
6–10 years	80 (29.5)	2 (15.5)	78 (30.2)	0.566	9 (17.4)	71 (32.4)	0.151
11–15 years	51 (18.9)	4 (30.7)	47 (18.2)		10 (19.2)	41 (18.7)	
≥16 years	54 (19.9)	3 (23.1)	51 (19.8)		14 (26.9)	40 (18.3)	
Type of insulin used							
Human insulin	12 (4.4)	0 (0.0)	12 (4.7)		1 (1.9)	11 (5.0)	
Insulin analogs	242 (89.3)	13 (100.0)	229 (88.7)	0.441	46 (88.5)	196 (89.5)	0.357
All insulin types	17 (6.3)	0 (0.0)	17 (6.6)		5 (9.6)	12 (5.5)	
Total daily insulin dose							
≤50IU	152 (56.1)	5 (38.5)	147 (57.0)	0.189	14 (26.9)	138 (63.0)	0.000*
>50IU	119 (43.9)	8 (61.5)	111 (43.0)		38 (73.1)	81 (37.0)	

TABLE 2. Continued

Variables/Test Value	N (%)	Lipoatrophy			Lipohypertrophy		
		Present N (%)	Absent N (%)	*p*	Present N (%)	Absent N (%)	*p*
Number of daily injections							
1	44 (16.2)	1 (7.6)	43 (16.7)	0.392	4 (7.7)	40 (18.3)	0.001*
2	71 (26.2)	6 (46.2)	65 (25.2)		5 (9.6)	66 (30.1)	
3	27 (10.0)	1 (7.6)	26 (10.0)		6 (11.5)	21 (9.6)	
4	129 (47.6)	5 (38.6)	124 (48.1)		37 (71.2)	92 (42.0)	
Current insulin therapy							
Prandial only	71 (26.2)	6 (46.2)	65 (25.2)	0.216	3 (5.8)	68 (31.1)	0.000*
Basal only	47 (17.3)	1 (7.6)	46 (17.8)		6 (11.5)	41 (18.7)	
Prandial and basal	153 (56.5)	6 (46.2)	147 (57.0)		43 (82.7)	110 (50.2)	
Number of injection sites							
1	75 (27.7)	6 (46.2)	69 (26.7)	0.251	20 (38.5)	55 (25.1)	0.147
2	113 (41.7)	6 (46.2)	106 (41.5)		17 (32.7)	96 (43.8)	
3	81 (29.9)	1 (7.6)	80 (31.0)		14 (26.9)	67 (30.6)	
4	2 (0.7)	0 (0.0)	2 (0.8)		1 (1.9)	1 (0.5)	
Status of performing regular systematic rotations							
No	81 (29.9)	7 (53.8)	74 (28.7)	0.212	23 (44.3)	58 (26.5)	0.000*
Different areas for each injection	104 (38.4)	2 (15.5)	102 (39.5)		10 (19.2)	94 (42.9)	
1 week in each area	21 (7.7)	1 (7.6)	20 (7.8)		0 (0.0)	21 (9.6)	
Random	65 (24.0)	3 (23.1)	62 (24.0)		19 (36.5)	46 (21.0)	
Status of performing regular intra-regional rotations							
Yes	111 (41.0)	0 (0.0)	111 (43.0)	0.002*	3 (5.8)	108 (49.3)	0.000*
No	160 (59.0)	13 (100.0)	147 (57.0)		49 (94.2)	111 (50.7)	

*$p < 0.05$

Of the lipohypertrophy cases, 12.6% were grade 1 and 6.6% were grade 2. In a study from Thailand, 21.5% of patients had grade 1 lipohypertrophy and 14.3% had grade 2 lipohypertrophy. In contrast, a study in Saudi Arabia reported that 57.5% of lipohypertrophy cases were grade 1 and 33.75% were grade 2.[6,17] In the present study, most of the identified lipohypertrophy cases were in an early stage, which is a favorable finding. Although our primary aim was to prevent lipodystrophies, the results were crucial for early diagnosis and effective intervention.

Notably, the duration of diabetes is not a risk factor for developing lipohypertrophy and lipoatrophy. Several studies have indicated a significant positive correlation between the duration of diabetes and prevalence of lipohypertrophy; however, some others have reported the opposite.[3,6,9,17,23,25–27] The duration of DM is a critical factor in starting insulin therapy. However, insulin therapy may be simultaneously started when DM is diagnosed. Therefore, it may be recommended to consider the duration of insulin therapy instead of the duration of diabetes.

No significant difference was found between lipohypertrophy and lipoatrophy in relevance with BMI. However, it was found that 84.7% of those with lipoatrophy and 82.6% of those with lipohypertrophy were obese or overweight. Obesity is a crucial risk factor of lipohypertrophy.[8,13,26,27] It is beneficial to evaluate individuals with high BMI in terms of lipodystrophy risk.

In the present study's sample, lipohypertrophy developed in 92.3% of those with an HbA1c >7% and lipoatrophy in 80.8%. Lipohypertrophy prevalence increases with HbA1c level.[3,8,9,26,27] The HbA1c level was found to be <7 mg/dL in 14.9% of the participants in a study by Sürücü and Okur Arslan and in 9.8% of the participants in a study by Ajlouni *et al*.[3,8] In a study by Barola *et al*., the average HbA1c level was 9.7 ± 2.6.[27] In the present study, the HbA1c of 18.5% of the participants was ≤7 mg/dL. Thewjitcharoen *et al*. and AlJaber *et al*. found that HbA1c level, and there was no significant correlation between the presence of lipohypertrophy supports our study.[6,17]

In this study, insulin therapy duration is not a risk factor for lipoatrophy and lipohypertrophy, and the total daily insulin dose is a risk factor for developing lipohypertrophy. Moreover, studies have revealed that using insulin for long periods[6,19,23,28] and at high doses is a risk factor of lipohypertrophy.[6,9,19,22,26–28] It is known that as the duration of insulin therapy is prolonged, insulin more possibly causes lipoatrophy and lipohypertrophy, as it has a multiplying effect on fat and triggers fatty tissue growth.[19] In the present study, patients with a total daily insulin dose >50 IU had a high lipohypertrophy prevalence (73.1%), which is attributed to the fact that they had been injecting high-dose insulin at a time, and drug edema in the injection site caused increased pressure and trauma around it.

A significant correlation was found between the number of daily insulin injections and lipohypertrophy. Several studies have determined that lipohypertrophy prevalence increased as the number of daily injections increased.[3,4,8] This may be due to increased insulin exposure and tissue trauma in addition to the potent growth hormone effect of insulin.

The individuals using prandial and basal insulin had a higher prevalence of lipohypertrophy. Studies have shown that the prevalence of lipohypertrophy is lower in individuals using only basal insulin than in those using both basal and bolus insulin.[4,8] In the present study, a high lipohypertrophy prevalence in individuals using prandial and basal insulin was considered to result from a higher number of daily injections in the injection site, thus a more severe tissue trauma and longer basal insulin absorption at that site.

Among patients who did not perform regular systematic and intra-regional rotation, lipohypertrophy prevalence was 44.2%, and lipoatrophy prevalence was 53.8%. The reason for this high rate in our study may be that repeated injections to the same injection area led to complications, including fatty tissue, pain, and scar tissue, and this results in fatty, hard, and swollen lesions under the skin. Additionally, these lesions impair insulin absorption, thus complicating diabetes management. Patients do not want to switch insulin injection sites because they feel less pain in the lipohypertrophic region.[3,4,6,8,9,19,25,29,30]

Research results in the literature indicated a significant relationship between lipohypertrophy and the type of insulin used.[6,8] However, no significant relationship was observed between the type of insulin used and lipoatrophy and lipohypertrophy. In the literature, a significant decrease was noted in the prevalence of lipodystrophy in 10%–55% of individuals diagnosed with diabetes who use >2% animal insulin per day. The prevalence of lipoatrophy with the use of recombinant insulins was reported to be only 0.2%–1.4%.[31]

This study was confined to individuals with diabetes who presented to a university hospital in a certain period; thus, the results can only be generalized to the respective population. The questions were created by the researchers as there is no scale for determining lipodystrophy in our country. As a descriptive study, the results show associations but do not prove causality. Individuals were selected using non-probability random sampling, which may have led to selection bias. Although lipodystrophies are most frequently evaluated by palpation and inspection in clinical practice, one of our limitations was that this method cannot be evaluated with ultrasonography, which provides a more objective evaluation, considering that this method may be low in terms of reliability.

CONCLUSIONS

The results of this study are crucial regarding identifying risk groups and developing necessary interventions. Although the findings of this study cannot be generalized, it revealed that the prevalence of lipoatrophy and lipohypertrophy has decreased in recent years in Turkey. Additionally, patients who did not perform regular and systematic intra-regional rotation, those aged ≤60 years, women, those using insulin at a dose of ≥50 IU, those administering injections four times/day, and those using prandial and basal insulin were at risk of developing lipohypertrophy and lipoatrophy. The results of the present study indicated that risk groups should be primarily screened regarding lipoatrophy and lipohypertrophy, training in safe injection practices should be provided periodically as part of diabetes education and counseling services to prevent lipodystrophy, and a standard scale should be established for determining lipodystrophy cases and be introduced to clinical practice.

CONFLICT OF INTEREST

There is no conflict of interest between the authors.

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