Research Paper

Prevalence of Insulin Injection-induced Lipodystrophy and Associated Risk Factors in Children and Adolescents With Type 1 Diabetes Mellitus

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ABSTRACT

Background: Lipodystrophy is the most common complication of insulin injection that has not been studied yet in children with type 1 diabetes mellitus (T1DM) in Isfahan.

Objectives: This study aimed to evaluate the prevalence of insulin injection-induced lipodystrophy based on related risk factors in children and adolescents with T1DM.

Methods: In this cross-sectional study, children and adolescents aged less than 18 years with T1DM who referred to the endocrinology clinic of Imam Hossein Hospital in Isfahan, Iran, in 2019 were enrolled. The baseline, anthropometric, and T1DM-related characteristics of the patients were recorded. Lipodystrophy was diagnosed by clinical examination. The characteristics of patients with and without lipodystrophy were compared. The association between lipodystrophy and disease-related factors was investigated.

Results: In this study, 194 patients with T1DM (88 boys and 106 girls) aged 3 to 18 years were evaluated. Lipodystrophy was diagnosed in 91 patients (46.9%), of which 64 patients (33%) had grade 1, 24 patients (12.4%) had grade 2, and 3 patients (1.5%) had grade 3 lipodystrophy. There was a significant difference in the frequency of lipodystrophy based on age, BMI, patient education, parent education, insulin injection site, duration of diabetes, injection site change, needle change, insulin dose, HbA1c, and hypoglycemia ($P<0.05$). Regression analysis indicated that there is a significant association between the presence of lipodystrophy and HbA1c ($P<0.001$, $t=7.20$), insulin dose ($P<0.001$, $t=4.47$), BMI ($P<0.001$, $t=3.78$) and duration of T1DM ($P=0.002$, $t=3.15$).

Conclusion: In this study, we reported a high prevalence of lipodystrophy among T1DM patients in Isfahan. From the studied risk factors, duration of diabetes, lower BMI, using a high dose of insulin, and uncontrolled diabetes (HbA1c>7) were the most important risk factors for lipodystrophy.

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Introduction

Type 1 diabetes mellitus (T1DM) is one of the most common endocrine disorders in children and adolescents that is caused due to the inability of the pancreas to produce insulin [1, 2]. The incidence of T1DM is constantly increasing in the world and is estimated that its incidence increases by 3.9% annually [3]. In epidemiological studies, the prevalence of T1DM in Iran has been reported from 13.35 per 100000 people in the southwest to 48 per 100000 people in the north [4, 5]. T1DM is associated with serious acute and chronic complications [1, 2]. Proper control of blood glucose is the most effective way to reduce the long-term complications of this disease [6].

Although the use of insulin is essential in T1DM patients, its injection can cause several skin problems. Many of these complications are acute and temporary such as bleeding, bruising, pain, inflammation, redness, and infection. Lipodystrophy is the most common chronic skin complication of insulin injection, which can manifest as either lipohypertrophy or lipoatrophy. Lipoatrophy means the loss of subcutaneous adipose tissue and is a disorder caused by an immunological response to insulin impurities. The prevalence of lipoatrophy has decreased with the purification of insulin and the presence of recombinant insulin and is estimated to occur in only 1-2% of insulin-injecting patients [6-8]. Lipohypertrophy manifests as subcutaneous adipose tissue swelling that can be hard or soft to the touch, with a prevalence of 20 to 70% reported in various studies [9]. Based on the results of a systematic review study, the prevalence of lipodystrophy is lower in patients with T1DM than in T2DM. The rate for T1DM had been reported between 19-49% in different studies [10]. In a study in Iran among a small sample size of T1DM patients, the rate was reported 39% [11].

Histologically, the hypertrophic adipocytes are twice as large as those from normal subcutaneous areas and contained numerous small lipid droplets. Electron microscopic analysis also revealed a minor population of small adipocytes, suggesting active differentiation or proliferation [12]. Several factors are reported to affect the development of lipohypertrophy, such as the period of insulin usage, gender, body mass index (BMI), injection site, recurrent tissue trauma from failure to rotate injection sites, and the frequency of needle reuse [13, 14].

The importance of lipodystrophy is that injection of insulin into a site of lipodystrophy may lead to erratic absorption of the insulin, with the potential for poor glycemic control and unpredictable hypoglycemia [12]. Early diagnosis of lipodystrophy is very important. Pain sensations diminish in areas where lipodystrophy has formed and for that reason, diabetic patients prefer to always administer their injections on the same site. As a result, lipodystrophic tissue increases [15].

Therefore, both healthcare providers and diabetics should be well aware of the importance of lipodystrophy. It is important to note that many of the skin complications of insulin injection are reduced by learning the correct insulin injection technique, which shows the important role of healthcare providers. Due to the above notes and also since this study has not been performed yet in the population of children with T1DM in Isfahan, we aimed to determine the prevalence of insulin injection-induced lipodystrophy and its related risk factors in children and adolescents with T1DM. However, our findings would help provide better management protocols in this field for T1DM patients.

Methods

In this cross-sectional study, children, and adolescents with T1DM aged less than 18 years who referred to the pediatric endocrinology clinic of Imam Hossein Children's Hospital in Isfahan in 2019 were enrolled. This study was conducted following the Declaration of Helsinki and approval for the study protocol was granted by the research ethics committee of Isfahan University of Medical Sciences with an ethical code of IR.MUI.MED.REC.1399.010 and research project number 398221.

In this study, children with T1DM for at least one year, aged less than 18 years old with no underlying and concurrent disease, and the exclusion criteria including any history of skin disorders, surgical operation with scars or trauma at insulin injection sites, and use of insulin pump were included.

Patients and their parents were informed about the goals and methods of the study and written informed consent was obtained before participating in the study. Information regarding the baseline, demographic, anthropometric, and disease-related factors including duration of diabetes, insulin injection site, insulin dose, injection site change, needle change, HbA1c, and hypoglycemia were obtained and recorded in a checklist. The checklist was prepared based on available questionnaires in this field [11, 15, 16]

Table 1. Characteristics of T1DM patients and those with and without lipodystrophy

Demographic Variables	Variables	Mean±SD/No. (%)			P*
		Lipodystrophy n=91	No Lipodystrophy n=103	Total T1DM Patients n=194	
Age (y)		11.8±4.5	11.2±3.6	11.53(4.06)	0.34
Gender	Female/male	54(59.4)/37(40.6)	52(50.48)/49.52)	106(54.6)/88(45.4)	0.21
Age group	<16 ≥16	63(69.23) 28(30.77)	87(84.46) 16(25.54)	150(77.32) 44(21.78)	0.01
Patients' education	-preschool -Elementary -Guidance school -High school	14(15.38) 31(34.1) 14(15.38) 32(35.13)	11(10.68) 46(44.66) 27(26.21) 19(18.45)	25(12.89) 77(39.69) 41(21.13) 51(15.99)	0.018
Parents' education	-Elementary/high school -Diploma -University	22(24.17) 44(48.35) 25(27.46)	17(16.50) 37(35.92) 49(47.58)	39(20.10) 81(41.75) 74(38.15)	0.016
Physical examination	BMI(kg/m^2)	18.5±4.2	20.5±4	-	0.001
Insulin injection site	-Arm -Abdomen -Thigh -Combined	19(20.87) 38(41.75) 22(24.17) 12(13.18)	31(30.10) 4(3.88) 10(9.71) 58(56.31)	50(25.77) 42(21.65) 32(16.49) 72(37.11)	<0.001
T1DM related factors	Duration of diabetes ≤5 years >5 years	45(49.45) 46(50.55)	85(82.52) 18(27.48)	130(67) 65(33)	<0.001
Mean duration of diabetes		5.4±3.5	3.6±2.9	-	<0.001
Insulin dose	≤0.7IU/kg >0.7IU/kg	6 85	34 69	40 154	<0.001
Mean insulin dose		1.2±0.4	0.8±0.2	-	<0.001
HbA1c	≤7 >7	8 83	46 57	54 140	<0.001
Mean HbA1c level		9±1	7.5±1.2	-	<0.001
Injection site change	-Unchanged -Accidental -Weekly -After each injection	26 33 14 18	2 16 55 30	28 49 69 48	<0.001
Needle change	-After each injection -After 2-3 injections -After 4-5 injections -Unchanged	2 27 32 30	18 57 20 8	20 84 52 38	<0.001
Hypoglycemia		51	15	66	<0.001

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by two pediatric endocrinologists (NM, EH), and was confirmed by experts in pediatrics endocrinology.

In this study, all patients used Novo rapid and Lantus insulin pens. Hypoglycemia was defined as the occurrence of one or more symptoms of hypoglycemia (such as palpitations, tiredness, sweating, strong hunger, dizziness, and tremor) and a confirmed blood glucose level of ≤60 mg/dL [13]. Also in the case of HbA1c, the patient's last test was used to record in the questionnaire. Lipodystrophy was evaluated by a pediatric endocrinologist during the follow-up period. Characteristics of T1DM patients with and without lipodystrophy were compared.

Evaluation of lipodystrophy

The presence of lipodystrophy was determined by clinical examination of the insulin injection sites by pediat-

Table 2. Association between the presence of lipodystrophy and T1DM-related factors

Variables	B	Std. Error	Beta	t	Sig.
BMI	-0.028	0.007	-0.237	-3.788	0.000
Insulin dose	0.333	0.074	0.257	4.477	0.000
HbA1c	0.152	0.021	0.412	7.200	0.000
Age	0.007	0.009	0.057	0.816	0.416
Duration of diabetes	0.030	0.010	0.204	3.154	0.002

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ric endocrinologists. Examinations took place in warm rooms (to avoid shivering) with oblique lighting to aid visual inspection and examiners' hands were washed and warmed. Light-to-moderate pressure with small sweeps of the fingertips was used to detect lipodystrophy lesions. Accordingly, lipodystrophy values were distinguished as follows: Grade 0=no change; grade 1=visible hypertrophy of fat tissue but with normal consistency on palpation; grade 2=intensive fat tissue thickening but with firm consistency; and grade 3=lipoatrophy [16].

Statistical analysis

Data were analyzed using SPSS software, version 21 (SPSS Inc. Chicago, IL, USA). Continuous and categorical variables were compared in two groups of T1DM patients with and without lipodystrophy using the student t-test and chi-square tests, respectively. Multiple logistic regression analysis was performed to determine the risk factors related to lipodystrophy in T1DM patients. P<0.05 was considered statistically significant.

Results

In this study, from 241 patients with T1DM who referred to the diabetes clinic, 194 patients (88 [45.4%] boys and 106 [54.6%] girls) were enrolled. The mean age of the study population was 11.5 (4.1) ranging between 3-18 years. The mean duration of T1DM in the studied patients was 4.5 (3.4) years. Lipodystrophy was presented in 91 (46.9%) of the patients. Grade 1, 2, and 3 of lipodystrophy was presented in 64 (33%), 24 (12.4%,) and 3 (1.5%) of the patients. Characteristics of T1DM patients with and without lipodystrophy are presented in Table 1.

The results of the study showed that the frequency of lipodystrophy was higher in patients over 16 years and patients with diabetes for more than 5 years (P<0.05). High school patients and patients with under-diploma parents were more likely to develop lipodystrophy (P<0.05). The highest frequency of lipodystrophy in patients was seen at the abdominal site (P<0.05). Patients who changed the injection site weekly and changed the insulin pen needle after each injection had the lowest incidence of lipodystrophy (P<0.05). Patients with uncontrolled diabetes (HbA1c >7%), patients who used higher doses of insulin (>0.7 U/kg), and patients with hypoglycemic attacks were more likely to develop lipodystrophy (P<0.05). There was no significant difference between girls and boys in terms of the presence of lipodystrophy (P>0.05).

The mean duration of diabetes, insulin dose, and HbA1c in patients with lipodystrophy were higher than in patients without lipodystrophy and the mean BMI was lower (P<0.05). Regression analysis indicated that there is a significant association between the presence of lipodystrophy and HbA1c (P<0.001, t=7.20), insulin dose (P<0.001, t=4.47), BMI (P<0.001, t=-3.78) and duration of T1DM (P=0.002, t=3.15) (Table 2).

Discussion

In this study, the prevalence of insulin injection-induced lipodystrophy and its associated risk factors in T1DM patients aged 3-18 years was investigated. The prevalence of lipodystrophy was 47% and most of the patients had grade 1 lipodystrophy. We found a significant relationship between lipodystrophy and the level of HbA1c, insulin dose, BMI, and duration of T1DM.

Evidence from different populations indicated that despite using recombinant human insulin, the rate of lipodystrophy is still high, which indicates the importance of other T1DM management factors [11].

Findings of different studies in this field indicated a wide range of lipodystrophy in T1DM patients. It ranges between 28-58.5% in different countries. The rate was

reported at 28.7% in Germany [16], 58.5% in Ethiopia [17], 48.8% in Turkey [15], 46.6% in Thailand [18], and 39.3% in a study in the north of Iran (Sari) [11]. There were few studies in this field among Iranian children and adolescents. As mentioned only in one study in Sari among a small sample size of T1DM patients (56 patients), the rate of lipodystrophy was 39.3% [11].

In the current study, the rate was 46.9% with superiority of its grade 1 form. Previous studies also reported that grade 1 lipodystrophy is the most common form of the disease and grade 3 is the rare form of lipodystrophy. Our finding in this field was similar to previous studies [11, 12, 16]. Tsadik et al. in Ethiopia have reported a higher rate of grade 2 lipodystrophy in the studied population [17]. It is suggested that a higher rate of grade 1 lipodystrophy may be due to using of human recombinant insulin.

In this study, the frequency of lipodystrophy was higher in patients over 16 years of age and high school patients, and there was no significant difference between girls and boys in terms of lipodystrophy. In this regard, Al Hayek et al. achieved similar results [12], but the results of the study of Hajheydari et al. showed that male patients, patients with lower education, and younger patients were more likely to have lipodystrophy [16].

In this study, the mean BMI was significantly lower in patients with lipodystrophy than in those without. Our result was similar to the findings of the study by Hajheydari et al. [16], but in the Vardar and Kizilci study, no significant difference was observed between patients in terms of lipodystrophy based on BMI [15].

Some previous studies also demonstrated that BMI is an effective factor in the development of the problem [11, 12, 15, 16]. In our study, we found a significant association between lipodystrophy and BMI.

Considering our findings and the results of previous studies among T1DM patients in our population that patients with poor glycemic control had lower BMI [19], and also the findings of the current study, it is suggested that there is a mutual association between the mentioned factors in T1DM patients which should be evaluated in future studies.

The study also found that increasing the duration of insulin usage increased the chances of developing lipodystrophy, which was similar to the results of the study of Al Hayek et al. [16] and Vardar and Kizilci [15].

In the present study, the highest frequency of lipodystrophy was seen in the abdominal region, as concluded by Hauner et al. [20]. However, Hajheydari et al. reported the highest frequency in the arm area, and the results of the study of Al Hayek et al. showed that the frequency of lipodystrophy was higher in the thigh area [15-17]. There are different reports about the most common site of lipodystrophy in different age groups. It seems that in children, the abdomen is the most common site because children used this site more easily for injections. However, the reports in this regard are not similar in various studies.

As reported by other similar studies, the frequency of lipodystrophy was higher in patients who did not change the insulin injection site weekly and changed the insulin needle frequently [13, 15, 21, 22].

Based on the findings of a study, 98% of patients with lipodystrophy did not change the injection site or inject the insulin incorrectly, and only 5% of patients who changed the injection site correctly developed lipodystrophy. Hajheydari et al. did not find a significant relationship between changing the location of insulin injection and developing lipodystrophy [16].

Another important factor influencing the development of lipodystrophy in our study was the rate of insulin needle change. This means that the lower the rate of insulin needle change, the higher the frequency of lipodystrophy, which was similar to the results of the study of Vardar and Kizilci [15] and Al Hayek et al. [16] Reuse of insulin needles leads to damage to the needle tip and loss of its silicone coating, which in turn leads to subcutaneous fat damage and lipodystrophy [14, 15].

Our findings showed that in patients with lipodystrophy, the mean level of HbA1c, poor control diabetes, and mean dose of insulin use were significantly higher than those without lipodystrophy. The rate of hypoglycemia was significantly higher in patients with lipodystrophy tin in patients without lipodystrophy. Other studies also reported a higher rate of unexpected hypoglycemia in patients with lipodystrophy [18, 23-25].

Blanco et al. demonstrated that the rate is six times higher than those without lipodystrophy [13]. Thewjitcharoen et al. have reported a 7 times higher rate of hypoglycemia in T1DM patients with lipodystrophy [18].

However, it seems that there is a mutual association between inappropriate glycaemic control and high dose of insulin use in T1DM and lipodystrophy.

Considering the results of the current study, it seems that pediatric endocrinologists or diabetes nurses, or any other healthcare professionals involved in the management of T1DM patients could classify their patients based on the mentioned factors as high or low-risk patients for the development of lipodystrophy and provide planned education to the patients and their family. It seems that the patients should also be trained in the identification of lipodystrophy and the correct technique of insulin injection.

The limitations of the current study were its cross-sectional design and small sample size. Further, considering that the gold standard method for diagnosis of lipodystrophy is ultrasound [26], cases with subclinical lipodystrophy specially lipohypertrophy may be missed by clinical diagnosis (observation and palpation) and it is suggested that the rate may be underestimated.

Though, it seems that prospective as well as interventional studies with a large sample size of T1DM patients would provide us with more accurate findings in this field. The strength of our study was that it was the first study in Iran with an acceptable sample size that evaluated the prevalence of this disease in T1DM patients.

Recently, Singh et al. evaluated the association of inflammatory factors including serum TNF-α, IL-1β, and anti-insulin antibodies with lipodystrophy. They indicated that both the insulin injection technique and the level of the mentioned inflammatory factors are associated with the development of T1DM patients [27]. It is recommended to investigate the role of these factors in this field in our population.

Conclusion

In this study, we reported a high prevalence of lipodystrophy among T1DM patients in Isfahan. From the studied risk factors, duration of diabetes, lower BMI, using a high dose of insulin, and uncontrolled diabetes (HbA1c >7) were the most important risk factors for lipodystrophy. Given that most lipodystrophy-related risk factors are associated with better management of the disease, it is necessary to train patients, their parents, as well as health workers about the risk factors associated with lipodystrophy and try to provide an appropriate management system for T1DM to achieve better glycaemic and metabolic control for the patients.

Ethical Considerations

Compliance with ethical guidelines

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (IR.MUI.MED.REC.1399.010) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was also obtained from all individual participants involved in the study.

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Authors' contributions

All authors equally contributed to preparing this article.

Conflicts of interest

The authors declared no conflict of interest.

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