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Insulin-induced lipodystrophy and predisposing factors in children and adolescents with type 1 diabetes mellitus (T1DM) in a tertiary care Egyptian center

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Abstract. *Background:* Lipodystrophy (LH) is one of the most common complications of subcutaneous insulin injection. Many factors are incriminated in the evolution of LH in children with diabetes type 1 (T1DM). LH may affect insulin absorption in skin areas involved, resulting in negative impact on blood glucose levels and glycemic variability. *Patients and Methods:* We calculated evaluated the prevalence of LH in relation to possible clinical factors associated with the development of LH in a cohort of children (*n* =115) with T1DM using insulin pens or syringes and we studied possible predisposing factors including their age, duration of T1DM, injection technique, insulin dose/kg, degree of pain perception, and HbA_{1c} level. *Results:* In our cross-sectional study, 84% of patients were using pens for insulin injection and 52.2 % of them were rotating the site of injection on daily basis. 27 % did not experience pain during injection while 6 % had the worst hurt. 49.5 % had clinically detectable LH. Those with LH had higher HbA_{1c} level and more unexplained hypoglycemic events compared to those without LH (P: 0.058). The hypertrophied site was related to the preferred site of injection which was the arms in 71.9 % of the cases. Children who had LH were older with longer duration of T1DM, rotating sites of injection less frequently and were more frequently reusing needles compared to children without LH (P: < 0.05). *Conclusion:* Improper insulin injection technique, older age, and longer duration of T1DM were associated with LH. Proper education of patients and their parents must include correct injection techniques, rotating injection sites, and minimal reuse of needles. (www.actabiomedica.it)

Key words: Insulin, lipohypertrophy, children, adolescents, prevalence, risk factors

Introduction

Lipodystrophy (LH) is a common dermatologic problem that occurs in patients with diabetes on insulin therapy. which can manifest as either lipohypertrophy or lipoatrophy (1).

This condition, affecting subcutaneous adipose tissue, can be classified into lipohypertrophy (LH) and lipoatrophy (LA). Both are characterized by different pathogenetic mechanisms and prevalence. LH is more common than LA (2,3) and is characterized by local accumulation of fat tissue in a subcutaneous insulin

injection site. Its prevalence varies from 20 to 70% (4). LA is characterized by loss of subcutaneous adipose tissue and is a disorder caused by an immunological response to insulin impurities. The prevalence of LA 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 (5,6).

Pathogenic mechanisms of LH are still uncertain, but repetitive mechanical trauma derived from needle use and local trophic effects of insulin might produce an excessive fat tissue growth (7).

Moreover, several factors are reported to affect the development of LH, such as: longer duration of insulin therapy, high insulin dose per kg, gender, injection site, recurrent tissue trauma from failure to rotate injection sites, and the frequency of needle reuse (1,8,9). In addition, other proposed factors include obesity, poor patient education, and poorly controlled diabetes. It has been advocated that the use of insulin analogs with multiple daily insulin injections (MDI) and the use of insulin pumps (continuous subcutaneous insulin infusion (CSII) may decrease the risk of LH compared to those using human insulin and twice daily insulin injections (10-12).

Lipodystrophy may affect insulin absorption in skin areas involved, resulting in negative impact on blood glucose levels and glycemic variability (13-16).

Despite the important negative consequences of LH in children and adolescents, there are few recent data about its occurrence in children and adolescents in the developing countries (17) as well as great variability among the published studies (8-12,15,16).

The main aim of this study was to determine the prevalence of LH and other dermatologic abnormalities related to insulin injection in a large cohort of selected children and adolescents with type 1 diabetes mellitus (T1DM). Predisposing conditions associated with its development were also evaluated.

Patients and Methods

This cross-sectional study was performed, from1-2020 to 1-2022 on a sample of 115 randomly selected children and adolescents (47 female and 68 male) with T1DM, using insulin pens or syringes for more than 1 year. All subjects were followed at Pediatric Endocrinology and Diabetology Unit, Faculty of Medicine, Alexandria University, Egypt.

Clinical assessment was done during their routine outpatient clinic and included: patients' age, weight, height, body mass index (BMI), history of the disease, duration of diabetes, needle length, type and dose of insulin requirements. Other possible risk factors including glycemic control, assessed by glycosylated hemoglobin (HbA_{1c}), frequency of reusing the needles for injection, frequency of rotating sites of insulin injection and preferred sites of injection. Needle use frequency was assessed asking "how many insulin injections were administered with the single needle/syringe". Correct site rotation was defined as injections within any half or quadrant with spacing of at least 1 cm for the subsequent injection and then moving to next half or quadrant in the following week.

Examination of the sites of insulin injection was ascertained by an expert trained diabetes nurse with inspection and palpation techniques with emphasis on presence of LH and associated skin complications including bruising, bleeding, infection, or discoloration.

LH was defined in presence thickened, swollen skin area, often associated with increased consistency on palpation, while depression at the injection site was suggestive of LA (18). Pain during injection was analyzed using Wong-Baker Faces Pain Rating scale (19).

Statistical analysis

Data are reported as mean ± SD, or as frequencies and percentages. Data were analyzed using IBMSPSS software package version 20.0 (Armonk, NY: IBM Corp).The Kolmogorov- Smirnov and Shapiro- Wilk tests were used to verify the normality of distribution of variables. Comparisons between groups for categorical variables were assessed using Chi-square test (Fisher or Monte Carlo). The student t-test was used to compare two groups for normally distributed quantitative variables. The Wilcoxon and Mann-Whitney test were used to compare groups not normally distributed. The significance of the obtained results was judged at the 5% level.

Ethics

All procedures were in accordance with the 1964 Helsinki declaration and its later amendments in October 2013 (www.wma.net). The study protocol was approved by the institutional review board of the college of medicine in Alexandria University (Egypt), and a written parental consent and child assent were obtained before performing the study (Registration number: 0303949).

Results

Demographic and clinical variables of the study population are presented in Table 1. The mean age of the diabetic patients was 10.1 ± 3.8 years with a mean diabetes duration of 4.4 ± 3.3 years. Their average HbA_{1c} level was 9.2 ± 2.2 %. Eighty-four (73%) were using pens for insulin injection and 52.2 % were rotating the site of injection daily. Sixty-seven per cent reported significant pain when using the same needle more than 4 times.

Patients who had LH were older, with longer duration of T1DM and higher HbA_{1c} versus patients without LH. They were rotating injection sites less frequently compared to patients without LH (P: < 0.05).

Lipohypertrophy was related significantly to the duration of diabetes and needle length (6mm) but not to the dose of insulin units per kg of body weight. However, the BMI-SDS of the LH group was significantly higher than those without LH nor to the BMI of the patient. HbA_{1c} levels of patients with lipohypertrophy did not differ from diabetics without LH. However, the incidence of hypoglycemia was higher in the LH group (Table 1).

LH was found (by palpation) in 57 cases (49.5%), bruising in 53.9 %, and skin discoloration in 31.3 %. children and adolescents reported LH at multiple sites. The mean diameter of the palpated lesions was 1.6 ± 0.6 cm. LA was found in 1/115 patients (0.8.%). The reuse of needles was significantly higher in the LH group vs the non-LH group. Only 12.3% of patients with LH failed to rotate the injection sites. A higher frequency of LH was observed in the arms (*n* = 41,

Table 1. Demographic and clinical variables of the study population. Values are expressed as mean ± SD and percentage.

	Total (n = 115)	**Presence of lipohypertrophy**		**P value**
Demographic and clinical variables		**Yes (n = 57)**	**No (n = 58)**	
Age (years)	10.1 ± 3.8	10.8 ± 3.4	9.3 ± 4	**0.048**
Sex				
Male	68 (59.1%)	33 (57.9%)	35 (60.3%)	0.071
Female	47 (40.9%)	24 (42.1%)	23 (39.7%)	
Duration of T1DM (years)	4.4 ± 3.3	5.2 ± 3.3	3.6 ± 3.2	**0.003**
BMI-SDS	0.54 ± 0.2	0.53 ± 0.25	0.45 ± 0.24	**0.03**
Dose of insulin (Units/kg/day)	1 ± 0.6	1.1 ± 0.8	0.9 ± 0.3	0.29
Overall prevalence of hypoglycemia < 4 mmol/L/3 months	5.35 ±1.8	5.8 ± 1.3	5.0 ± 2.1	**0.01**
Last glycosylated hemoglobin (HbA1c %)	9.2 ± 2.2	9.6 ± 2.4	8.8 ± 2	0.058
Pens or syringes (*)				
Needle length (mm) **4 mm** **6 mm**	 49 66	 18 39 (68%)	 31 27 (46%)	 **<0.01**
Pens	97 (84.3%)	45 (78.9%)	52 (89.7%)	0.11
Syringes	18 (15.7%)	12 (21.1%)	6 (10.3%)	

Legend: T1DM = Type 1 diabetes mellitus, BMI-SDS = body mass index standard deviation score,

71.9 %) followed by thigh area (*n* = 18, 31.6%) and abdomen (*n* = 10, 17.5%) (Table 2).

The pain score of patients with LH was significantly higher (when using normal skin areas) versus those without LH. The pain rating score was significantly lower in patients with LH (injecting in the LH areas) versus those without LH (Table 3).

Discussion

Marked variabilities have been detected in the prevalence of LH in different studies. These varieties of LH can partially be explained by the different risk factors.

In our study, the prevalence of LH in children and adolescents with T1DM was higher (49.5%) compared to published reports from Turkey (17.1%), United Arab Emirates (UAE) (39%), Saudi Arabia (23.7%) and Netherland (38.8%) (20-23). However, studies from India (62.1%) and Ethiopia (58.5%) reported higher prevalence of LH in their diabetic children (3,17).

In our study, as reported also by others, patients with longer duration of diabetes, repeatedly use of the same insulin needle more than 5 times, who lacked or infrequently rotated insulin injection sites, or requiring higher insulin dose/kg had higher risk for developing LH. Furthermore, they lower threshold of pain to injection may have encouraged them to use the LH sites for injection because these sites have decreased pain sensation. Therefore, it is crucial to try and systematically identify as many LH areas as possible to educate patients to prevent poor insulin injection habits.

In addition, relatively poorer glycemic control (higher HbA1c), and higher glucose variabilities measured by continuous glucose monitoring, with recurrent hypoglycemia and hyperglycemia appeared to be the negative consequences of using the LH site for repeated injections (3,17, 24,25). Other studies have stressed the importance of the low level of patients' education in increasing the prevalence of LH (26).

Due to the highly variable morphological characteristics of LH in terms of size, texture, and prominence of the skin, the experience of the observer and the method used for detecting LH may markedly affect the prevalence of LH.

A detailed description to identify LH lesions has been reported by Gentile et al (27). Skin ultrasound scans (US) is considered the gold standard but is too expensive for screening purposes (28).

The pathogenesis of LH lesions is characterized by the formation of fibrous and poorly vascularized lesions in the subcutaneous adipose tissue. Two important combined factors are important causative factors. The direct anabolic effect of insulin on local subcutaneous fat (leading to fat and protein synthesis) which is enhanced by the repeated injections (trauma) at the same site and/or repeated use of blunt needles (more trauma). This local trauma is exaggerated by using a small area of the skin without proper rotation of injections. In support of this view, other evidence of trauma to the site of injection (more bruising and discoloration) has been detected in our patients with LH versus those without LH.

Table 2. Frequency of lipohypertrophy at the different injection sites. Values are expressed as mean ± SD.

	Total (n = 115)	**Presence of lipohypertrophy**		**P value**
Lipodystrophy site		**Yes (n = 57)**	**No (n = 58)**	
• **Arms**		41 (71.9%)		
• **Abdomen**		10 (17.5%)		
• **Thigh**		18 (31.6%)		
Rotating sites	106/115 (92.2%)	50/57 (87.7%)	56/58 (96.6%)	0.43
No. of insulin injections/ day	3.3 ± 1.1	3.2 ± 1.2	3.5 ± 1.1	0.10
Needle reuse	4.2 ± 1.5	4.4 ± 1.7	3.9 ± 1.2	0.07

Table 3. Pain Rating Score in children and adolescents with T1DM

Pain rating score	**Total (n = 115)**	**Presence of lipohypertrophy**		**P value**
		Yes (n = 57)	**No (n = 58)**	
0	31 (27%)	9 (15.8%)	22 (37.9%)	**0.001**
2	34 (29.6%)	14 (24.6%)	20 (34.5%)	
4	31 (27%)	21 (36.8%)	10 (17.2%)	
6	8 (7%)	7 (12.3%)	1 (1.7%)	
8	4 (3.5%)	1 (1.8%)	3 (5.2%)	
10	7 (6.1%)	5 (8.8%)	2 (3.4%)	

The relatively higher prevalence of LH in our children can be explained by their use of regular human insulin (e.g., Humulin R ®, Novolin R®, Velosulin BR ®, Actrapid ®). In support of this view, it was found that patients treated with multiple daily injections (MDI) had lower incidence of LH when using insulin analogs than human insulins. This can be explained by the fact that regular human insulin (e.g., Humulin R ®, Novolin R®, Velosulin BR®, Actrapid®) has slower absorption rate from the subcutaneous tissue of insulin (consisting of a high percentage of hexamers bound to a zinc molecule) and it takes 60–90 min for insulin hexamers to dissociate into dimers and monomers for absorption into the blood stream (more time for local action). In contrast the fast-acting insulin analogs (consisting of monomers with rapid dissociation and absorption) are absorbed within 10–15 min of a subcutaneous injection. This longer stay of insulin in the subcutaneous tissue appears to increase the possibility of developing LH by the proliferating effect of insulin on lipocytes (3,29).

Our children with LH had relatively poorer control of glycemia (higher HbA_{1c}) and more unexplained hypoglycemic events despite receiving a relatively higher insulin dose. Decreased/impaired and/or erratic insulin absorption from affected parts can explain the impaired control of glycemia, increased fluctuations in glucose levels, higher occurrence of hypoglycemia, as well as increased incidence of ketoacidosis (30,31).

Bochanen et al. (26) reported that the combination of using 4 mm pen needles and online education on injection techniques significantly reduced the number of people with severe hypoglycemic episodes in 146 patients with T1DM. At baseline, LH was present in 63.0%, with 51.4% injecting in zones of LH, 37.0% incorrectly rotating and 95.9% reusing needles. After the intervention, 7.5% were still injecting in a LH zone, 4.1% rotated erroneously and needle reuse reduced to 21.2%. There was also a significant reduction of unexplained hypoglycemia and high glucose variability, but no change in the HbA_{1c} level nor in the insulin needs were reported.

In addition, the bad cosmetic appearance of LH lumps, especially in adolescents, can markedly increase their psychosocial stress generated by the disease. A problematic additional factor for patients of all ages, but most difficult for adolescents (32,33).

Clinical guiding principles for insulin injection, including recommendations on administration techniques, have been released by the International Society for Pediatric and Adolescent Diabetes (ISPAD) (34,35). The best suggested preventive and beneficial strategies for insulin induced LH include rotation of injection sites with each injection and using a new needle for each injection.

Switching to continuous subcutaneous insulin infusion (CSII), and/or short acting insulin analogues are alternative methods (36,37). These lesions can sometimes spontaneously regress but use of small amounts of dexamethasone along with insulin injections was found to be beneficial (38). If conservative steps fail, then liposuction is an effective alternative (39).

In conclusion, the prevalence of LH in children and adolescents in our study was high (49.5%) and occurred more frequently in our children and adolescents with longer duration of T1DM, improper rotating the site of injection and less frequently changing the needle.

Based on our and previous studies we recommend that injection sites should be examined repeatedly at each clinic visit by the physician or specialized nurse for detecting possible LH. Diabetic patients and their parents should also be taught to examine the injection sites and how to distinguish LH. All patients must be advised not to use LH areas for injections until the skin returns to normal, that may take few months. Proper education of patients and their parents shall include correct injection techniques, rotating injection sites with each injection, and minimal reuse of needles. Moreover, patients should be educated about LH, its risk factors and consequences.

Conflicts of interest: Each author declares that he or she has no commercial associations (e.g., consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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