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(REVIEW ARTICLE)

Insulin-induced Lipo hypertrophy and factors affecting it in children and adolescents with type 1 diabetes mellitus: Review of Literature in the past 12 years

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Abstract

Lipohypertrophy (LD) is one of the most common complications of subcutaneous insulin injection. Many factors are convicted in the development and progress of LD in children with T1DM. Lipodystrophy can worsen glycemic control in these children.

This review aimed at summarizing these important epidemiological and clinical data to clarify the different aspects of this abnormality and its predisposing factors that are necessary for prevention, early detection, and proper management.

Methods: We searched PubMed, Google Scholar, Research Gate, and Scopus for research articles related to insulin-induced LD after 2010. 28 papers were found, reviewed, and analyzed.

Results: The prevalence of LD varied greatly between 17% and 75% and was significantly affected by different risk factors. The pooled prevalence of LD in children and adolescents (16 studies) was 45.16 % while the pooled prevalence in adults was 41.3%. The prevalence of LD in children appeared to be relatively higher in children compared to adults. The most critical risk factors detected in these studies included: the longer duration of diabetes and the reuse of insulin syringe > 5 times, lack of rotating insulin injection sites and or using a small area for injection, higher insulin dose/kg, the BMI, the location of injection (more LD in the abdomen, low level of patient education, higher insulin antibodies and poor control of diabetes. In addition, the method of detecting LD markedly affected the prevalence of LD.

Conclusion: Improper insulin injection technique and longer duration of T1DM were the most important risk factors associated with LD. Children with LD have poorer glycemic control and require higher doses of insulin per kg compared to those without LD.

Keywords: Lipohypertrophy; Insulin; T1DM; Children; Adolescents; Prevalence

1. Introduction

Lipohypertrophy (LD) is a common dermatological problem that occurs in diabetic patients with insulin. It appears as soft painless benign lumps on the skin. The occurrence of LD is linked with the lipogenic action of insulin at the site of repeated injections (trauma) in the subcutaneous tissue (1, 2).

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Several risk factors are suggested to increase the risk of developing LD. These include repeated use of insulin needles, not rotating the injection sites, using a small area of the skin for injections, longer duration of insulin use, and high insulin dose per kg, In addition, other proposed include obesity (high BMI), poor patient education, and poorly controlled diabetes. It has been advocated that insulin analogs with multiple daily insulin injections and insulin pumps (continuous subcutaneous insulin infusion (CSII) may decrease the risk of LD compared to those using human insulin and twice daily insulin injections (3, 4).

Recurrent hypoglycemia, poor glycemic control with fluctuations of blood glucose and using high dose of insulin have been attributed to erratic insulin absorption from LD affected areas (5).

Despite the important negative consequences of LD in children and adolescents, there is a shortage of information on children about the subject. We reviewed the recent literature (after 2010) on the epidemiology of LD in large cohorts of children, adolescents, and adults on insulin therapy. In addition, we reviewed the literature on the available methods of LD screening, important risk factors in its etiology, pathology, and pathogenesis of this disorder as well as possible preventive and curative trials.

2. Material and methods

2.1. Methods

Epidemiological and clinical data on LD in children and adolescents with T1DM are growing since 2000. New aspects including the change in the prevalence with the introduction of new insulin analogs and the use of insulin pumps, the occurrence of complications monitored by the continuous glucose monitoring machines (CGMS) and factors increasing the risk of developing the disease have been studied and updated in various parts of the world. In addition, different aspects of the screening, pathology and pathogenesis have been exposed.

This review aimed at summarizing these important epidemiological and clinical data to clarify the different aspects of this abnormality and its precipitating factors that are necessary for the prevention, early detection, and proper management.

The literature was searched including PubMed, Google Scholar, Scopus and Research Gate, for research articles related to Type 1 diabetes mellitus (T1DM) in children, adolescents and adults, including prevalence, and possible factors that may increase the risk of LD children in different countries. Search keywords included the following: "Type 1 and Type 2 diabetes mellitus", And insulin induced Lipohypertrophy, And insulin analogs, And CSII, And Continuous glucose monitoring (CGMS), And HbA1C, And Children, And Adolescents, And Complications, And Hypoglycemia, And Prevalence, And Trend, And Pathology, and Management.

Inclusion criteria for this article review encompassed those on insulin-induced LD in children, adolescents and adults, in relation to epidemiology, prevalence, trends, gender, BMI, insulin injection, rotation of injections, needle size, needle reuse, duration of diabetes, glycemic control, and diabetes education. All articles with publication dates before 2010 and health-related topics not listed in the inclusion criteria were excluded from the search. Additionally, all other forms of LD in children and adults were excluded. (Registration Number: 0305850)

3. Results and discussion

Insulin LD denotes a benign tumor-like swelling of fatty tissue at the injection site secondary to the lipogenic effect of insulin. Based on inspection and palpation LD can be graded as follows: grade 0 = no changes; grade 1 = visible hypertrophy of fat tissue but palpably normal consistency; grade 2 = massive thickening of fat tissue with firm consistency; and grade 3 = lipoatrophy. (6)

3.1. Prevalence of Lipohypertrophy

Lipohypertrophy represents the most common cutaneous complication of insulin therapy. Despite improvements in insulin purity, the use of recombinant human insulin, and new injection techniques (pens, CSII) its prevalence remained high. The prevalence of LD varies considerably among different studies.

Table 1 summarizes 16 studies, on children and adolescents, from 11 countries after 2010 (Italy, India, Turkey, UAE, Saudi Arabia, Egypt, Canada, The Netherland, Iran, Austria and Ethiopia) after 2010. In these studies. the prevalence of

LD varied greatly between 17% and 62% and was significantly affected by different risk factors. The pooled prevalence of the studies using MDII and CSII (16 studies, n= 3208 children, and adolescents, 1449 had LD) was 45.16 %.

Table 1 Prevalence of LD and risk factors affecting its development in Children and adolescents in different studies (countries)

Authors-Year Location	**Study -Type Injection Type**	**Number- Age Duration of insulin use**	**Prevalence of LD**	**Significant Risk factors for LD detected**
Lombardo et al 2022 (7). Italy	CS 43% MDT 57% CSII	N= 212 11.9 ± 4.7 year 4.8 ± 3.4 years	44% palpation MDI 49% of 44% CSII 51% of 44%	Improper rotation of insulin administration low awareness on LD and age
Sharma et al 2022 (8). India	One-center Longitudinal 78% were reusing needles > 3 times.	N= 121 children (<15 years)	After 3 months of needle reuse, 91.3% had LD	Frequency of reuse positively correlated with local redness, bleeding, and leakage of insulin. LD reduced with single use
Barola et al 2018 (9). India	One center CS	N= 372 Mean = 17.1 years >3 months	62.1% palpation	Injections over smaller area (≤8.5 × 5.5 cm) and non-rotation of sites were found to be strongest independent predictor of LD. LD was reduced to half with bolus doses of rapid-acting insulin analogs than regular insulin
Conwell et al 2008 (10). Canada	CS single center CSII	N= 50 T1DM 13.3 +/- 3.5 years 2.8 +/- 1.7 years	Subcutaneous nodules = 62%, LD =42% palpation	Infusion sets inserted at 90 degrees were associated with lower LD scores.
Deeb et al 2019 (11). UAE	CS single center MDI and CSII	N= 104 T1DM Children 50 on CII	39% Palpation	An association was seen between LD and rotation frequency in children
Demir et al 2022 (12). Turkey.	Questionnaire Single center	N= 245 T1DM 14.9 ± 4.7 years 7.3 ± 4.1 years	MDI = 17.1% CSII = 4.6%	Higher doses of insulin Positive correlation between LD and BMI-SDS
Munster et al 2014 (13). Netherland	CS Single Center	N= 231 T1DM 14+/- 7 years	34.8%	Lipohypertrophy was associated insufficiency of alternating administration sites.
Hayek et al 2016 (14). Saudi Arabia	Single center CS	N= 174, 15.47 +/- 2 years 6.1 ± 4.5 years	23.7%	LD was associated with higher BMI, higher HbA1c, higher number of injection sites, higher rate of needle reuse and failure to alternate the injection site.
Yousef et al 2016 (15). Egypt	Single center CS	N= 152 8.4 +/- 3.2 years T1DM 2.80 ± 2.86 years	28.9%	

Omar et al 2011 (16). Egypt	Single center CS Pens/syringes	N= 119 1-21 (mean 10 years) T1DM Palpation	54.9%, Males =62.7% Females = 48.4%	LD was significantly associated with the duration of diabetes and the BMI. LD was associated with the use of higher dose of insulin
Tsadik et al 2018 (17). Ethiopia	Single center CS Pens/syringes	N= 176 Children T1DM	58.5%	Being younger, failure to rotate the injection site every week and multiple reuses of insulin syringe had significant influence on LD. LD was associated with the use of higher dose of insulin
Mostofizadeh et al 2018 (18). Iran	Single center CS Pens/syringes	N= 194 Children 3 - 18 years T1DM	46.9%	Significant association between LD and HbA1c, insulin dose, BMI and duration of T1DM
Singha et al 2018 (19). India	Single center CS Pens/syringes	N= 95 children, adolescents T1DM	45.2%	Improper injection site rotation technique. Serum TNF-α, IL-1β, and anti-insulin antibody levels; HbA1c; and high insulin dose /kg were higher in LD
Kalra et al 2018 (20). Multi-country	Multi-Country Survey Pen/syringes	N= 898 Palpation Children <18 years	45.6%	poor injection rotation, excessive needle reuse, and incorrect needle length choices
Schober et al 2009 (21). Austria	Single Center CSII	N= 78 Children	42%	
Personal data Shayma et al (Unpublished data) 2022 Egypt	Single center CS Pens/syringes	N= 115 10.1+/- 3.8 years 4.4 +/- 3.3 years	49.5 %	LD occurred more in older children with longer duration of DM and who were rotating sites of injection less frequently compared to children without LD

Table 2 Prevalence of LD and risk factors affecting its development in adults in different studies and countries

Authors-Year Location	**Study -Type Injection Type**	**Number- Age Duration of insulin use**	**HbA1C % Prevalence of LD**	**Significant Risk factors for LD detected**
Ucieklak et al 2022 (22). Poland	Cross sectional (CS) CSII	N= 79 24-30 years 9-20 years	6.7: 8.1 % 95% US 75% palpation	A higher dose of insulin per kg (>0.7U/kg)
Korkmaz et al 2021 (23). Turkey	Cs MDT	N= 136 53± 15 years 15.7±9.2years	-- 85% US	Total cholesterol level high insulin dose and coronary artery disease (CAD)
Hewjitcharoen et al 2020 (24). Thailand	CS Pen/syringe	N= 56 65.6±15.4 years 10 years	7.9±1.6% 46% palpation	The duration of insulin use (≥10 years), use of human insulin, and incorrect rotation of injection sites

Aljaber et al 2020 (25). Saudi Arabia	Multicenter CS Syringe/pen MDI	N = 202 58.5+/- 11 years 17 +/- 8 years	9.3 +/- 1.7% 39.7 % palpation	patients who used alcohol swabs had 2.6 times risk Patients who used more than 60 units/day
Blanco et al 2013 (26). Spain	CS pens	N= 430 adults	-- 64.4% palpation	non-rotation of sites, needle reuse > 5 times
Ji et al 2017 (27). China	CS	N= 401 59.5 ± 11 years	8.2% 53% palpation	weight-adjusted insulin dose and incorrect site rotation BMI, needle reuse frequency, and PNR remained modestly associated with LD prevalence
Frid et al 2016 (28). 42 countries	Multicenter CS	N= 13,289 All ages using insulin injections	--- 30.8% palpation	incorrect rotation of injection sites, use of smaller injection zones, longer duration of insulin use, and reuse of pen needles
Deng et al 2017 (29). Asia and Europe	Metanalysis 26 studies	N= 3231 T1DM All ages	-- pooled prevalence = 34% palpation	
Wang et al 2021 (30). Africa, Europe, Asia	Metanalysis 45 studies	N= 26,865 T1DM and T2DM on insulin All ages	-- Pooled prevalence T1DM= 40% T2DM = 46%	Pooled prevalence of LD in Europe = 44.6% in Africa = 34.8% and in Asia = 41.3%
De Coninck et al 2010 (31). 16 countries	Questionnaire Multicentre Syringe/pen	N= 4352 T1DM and T2DM All ages 171 centers in 16 countries	8.14 +/- 1.67 Adults =45.5% Adolescents =69.7% Children =57% Younger subjects having smaller LD lesions	Most LD lesions occur around injections sites on the abdomen and thighs, and least likely on the buttocks Higher mean HbA1c levels recorded in those who sometimes or often injected into the LD lesions
Bochanen et al 2022 (32). Belgium	Intervention study single use of 4 mm needles combined with education about injection technique	N= 146 All ages	63% before intervention 51.4% injecting in zones of LD, 37.0% incorrectly rotating and 95.9% reusing needles	Outcome of the study: The number of participants with severe hypoglycemia (from 15.8% to 4.1%, $p < 0.001$), unexplained hypoglycemia (from 46.6% to 16.4%, $p < 0.001$) and high glucose variability (from 64.4% to 29.5%, $p < 0.001$) was significantly reduced.
Pozzuoli et al 2018 (33). Italy	Single center CS	N= 352 68 ± 12 years T1DM and T2DM	-- 42.9%	the strongest correlates of LD were not spacing injections and not rotating the site of injection. Increasing doses of insulin and longer duration of insulin therapy increased the risk of LD

Table 2 summarizes the prevalence of LD in diabetic adults on insulin therapy (n =12), including metanalysis and multi-country studies (n = 48992, using MDIT and pens, 20239 had LD) the prevalence varied between 30.8% to 75% (palpation method) and even higher using ultrasonographic method (up to 95%).

The pooled prevalence of LD was 41.3%. The prevalence of LD is significantly higher in children compared to adults (z is -4.27, p < .00001). The pooled prevalence of LH in All ages (children, adolescents, and adults) (28 studies) was 44.9%.

4. Review and Discussion

Insulin-induced Lipohypertrophy lesions typically present as soft dermal nodules like lipomas or fibro collagenous scar tissue within the skin and can largely differ in size from a few mm to an orange size (34, 35).

LD lesions are characterized by fibrous and poorly vascularized lesions in the subcutaneous adipose tissue probably caused by the combined direct anabolic effect of insulin on local skin (leading to fat and protein synthesis) enhanced by repeated injections at the same site. The delineation between the dermal layers was disrupted in all current injection sites with increased dermal thickness compared to non-injected skin (36).

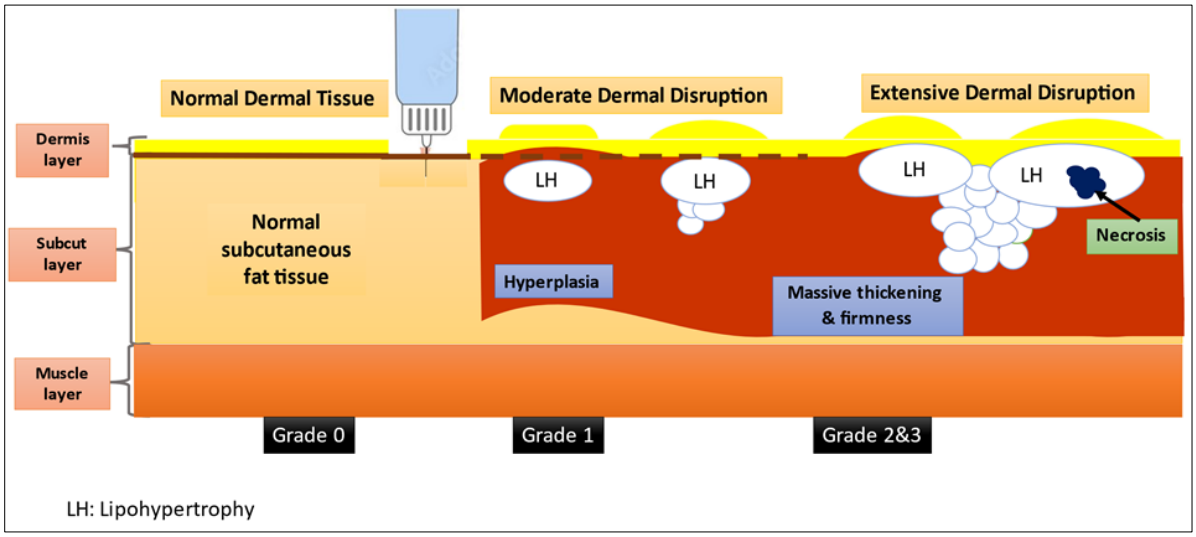

Figure 1 Illustration of the lipogenic effect of insulin injection in normal subcutaneous fat tissue; Grade 0: Normal dermal and subcutaneous tissue thickness and differentiation; Grade 1: Subcutaneous fat hyperplasia with nodule formation; Grade 2&3: Massive thickening with an extensive disruption in dermal and subcutaneous layers associated with reduced blood flow indicative of necrosis.

Figure 1 Grading of insulin- induced subcutaneous Lipohypertrophy

Histologically the hypertrophic adipocytes are twofold as large as those from normal subcutaneous areas and contained plentiful small lipid droplets. Electron microscopic analysis also showed a minor population of small adipocytes, suggesting active differentiation or proliferation. The appearance of collagenous scar tissue with hypo-vascular collagen and bland-looking fibroblasts has also been described (37, 38). (Figure 1)

Initial skin changes can be subtle and manifest only as the thickening of the skin. This can be easily missed by visual inspection and so areas should be palpated. It is recommended that to feel subtle skin thickening, the hand should be stroked firmly in a sweeping motion rather than using traditional techniques of light and deep palpation (39, 40).

In this review marked variabilities have been detected in the prevalence of LD in different studies. These variabilities can partially be explained by the different contributions of risk factors. Important risk factors found in these studies included: the longer duration of diabetes, the reuse of insulin syringe > 5 times, lack of rotating insulin injection sites, using a small area for injection, higher insulin dose/kg, BMI, the location of injection (more LD in the abdomen), low level of patient education, higher insulin antibodies and poor control of diabetes. In addition, the method of detecting LD markedly affects the prevalence of LD, and ultrasound detection increased markedly the diagnosis of LD in these patients compared to palpation and inspection (41-44).

The higher prevalence of LD in children versus adults can be explained by two factors. The relatively small area for injection in children versus adults, and the higher insulin-induced lipogenesis in young children compared to adults (45).

Moreover, it appears that pain threshold may be lower in young children compared to adults. This can increase their tendency to use the LD areas (with less pain sensation). Three studies found that younger children (6-8.12 years) were more sensitive to noxious stimuli than older children (9-14 years) (46).

Furthermore, the risk of LD in patients treated with MDI was described to be lesser when using insulin analogs than human insulin. This can be explained by the fact that regular human insulin (e.g., Humulin R, Novolin R, Velosulin BR, Actrapid) has a 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 bloodstream. In contrast, 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 LD (47,48).

Diagnostic methods affected markedly the detection of LD in the same cohort of patients. The relatively recent use of ultrasonography perceived more cases of LD than using inspection and palpation. In addition, experienced observers (e.g., nurses, and physicians) detect more LD lesions compared to non-experienced observers. Using ultrasonography, LD lesions appear as hyperechoic spots (fibrotic component) in diffuse areas of the subcutaneous tissue at the insulin injection sites. Sometimes the LD lesions appear as well-defined nodules with confined borders (edema and/or fluid components) lacking capsule or vascularity (49-51).

The echo signature for LD is described as well-circumscribed hyperechoic foci with defined borders or a nodular shape with a hypoechoic halo, heterogeneous in echotexture compared with surrounding tissue, associated with distortion of surrounding connective tissue in the absence of vascularity and absence of capsule. A relatively recent study confirmed that insulin-exposed tissue changes are heterogenous, and the authors provided a theoretical grading system for categorizing these changes (52, 53).

Because injecting insulin in LD lesions is less painful than injecting in normal skin, many patients prefer injecting their insulin in the LD areas. Unfortunately, injecting insulin in the LD regions is associated with a reduction of insulin absorption by up to 25% and an alteration of its duration of action. Subsequently, a significant increase in insulin dose is required to improve glycemic control (54, 55).

Many undesirable effects of LD have been documented in different studies. These include the bad cosmetic appearance of LD lumps and decreased/impaired and/or erratic insulin absorption from affected parts. This erratic absorption leads to fluctuation in glucose levels with a higher occurrence of hypoglycemia, and increased incidence of ketoacidosis (56, 57, 58).

Although repeated use of insulin needle has been associated with more LD and pain during injection by some, other researchers did not find significant difference in needle reuse between the patients with or without LD (16, 59,60).

5. Management of LD (Prevention and treatment)

The best suggested preventive and beneficial strategies for insulin-induced LD include rotation of injection sites with each injection and using a new needle for each injection. Switching to CSII2, and/or short-acting insulin analogs are alternative method. These lesions can sometimes spontaneously decrease in size and regress but the use of small amounts of dexamethasone along with insulin injections was found to be beneficial. If conservative steps fail, then liposuction is an effective alternative (61-66).

An intervention study by Bochanen et al 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 DM. At baseline, LD was present in 63.0%, with 51.4% injecting in zones of LD, 37.0% incorrectly rotating and 95.9% reusing needles. After the intervention, 7.5% were still injecting in an LD zone, 4.1% rotated erroneously and needle reuse reduced to 21.2%. There was a significant reduction of unexplained hypoglycemia and high glucose variability but no change in the HbA1c level nor in the insulin needs (67).

6. Conclusion

The pooled prevalence of LD in children and adolescents (16 studies, n= 3208 children, and adolescents, 1449 had LD) was 45.16 %. It appears clearly that insulin-related LD is still a common problem in children and adolescents with T1DM. In the majority of studies LD has been significantly related to older age, longer duration of DM, improper rotating the site of injection and less frequently changing of the needle.

Recommendations

Based on our data 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 LD. Diabetic patients and their parents should also be taught to examine the injection sites and how to distinguish LD. All patients must be counseled not to use LD areas for injections until the skin returns to normal, which may take a 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 LD, its risk factors, and its consequences.

Compliance with ethical standards

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Disclosure of conflict of interest

There is no conflict of interest among authors.

Statement of ethical approval

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