



(REVIEW ARTICLE)



Insulin-induced lipohypertrophy and factors affecting it in children and adolescents with type 1 diabetes mellitus: Review of the literature from the past 12 years: An appraisal and extension to adult subjects

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Abstract

Our research group has dealt with injection-induced lip hypertrophy (IILH) in insulin-treated subjects for over a decade, focusing on causes and consequences, education, prevention and treatment, comorbidities, and related complications. Stimulated by an excellent Review that recently appeared on the pages of this Journal, we want to contribute insight into IILH. This brief Commentary underlines some key concepts on how to identify, prevent and cure them, pointing out salient aspects derived from our research to provide the scientific community with an as complete as possible overview of evidence-based knowledge and highlight the need for further experimental insights.

Keywords: Diabetes mellitus; Insulin injection; Injection technique; Lipodystrophy; Lipohypertrophy

1. Introduction

This Journal has recently published an interesting review of the studies from the last 12 years cited on major international scientific databases (1) concerning risk factors and metabolic consequences of skin injection-induced lipodystrophies (in particular lipohypertrophies [IILH]) in insulin-treated children and adolescents compared to adults with type 1 diabetes mellitus (T1DM) on pens, syringes and insulin pumps (CSII). The analysis is detailed, and the conclusions agree with most papers dealing with the subject

Aim

For years our research group has published on IILH in different adult groups with T1DM and T2DM, including special populations such as older people (2) and those on dialysis (3-6). We dealt with methodological (7-10), epidemiological (11-13), pathophysiological (14), and educational (15,16) aspects and described metabolic consequences (11-14,16), associated comorbidities, acute and chronic complications (17-20), and costs (16,17) of IILH. Besides describing peculiar clinical cases (21,22), we commented on clinical trials and investigations from other groups (23-32), produced recommendations and guidelines on correct injection technique implementation to avoid lipodystrophies (LD) and especially IILH (9,33,34). Consequently, the abovementioned review has prompted us to provide our experience accumulated during the same 12-year period, to further contribute to an in-depth insight into the topic.

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2. Methods

The review by Soliman et al. (1) had already surveyed all the articles related to these items in children, adolescents, and adults. Therefore, our search located only the articles published by our group after 2010 on observational, retrospective or prospective, randomized, case-control, and structured-education intervention trials not included in that review as exceeding the specific Authors' interest.

To delve into the factors associated with IILH in agreement with the paper from Soliman et al., we considered research articles listed during the last twelve years on PubMed, Google Scholar, Scopus, and Research Gate related to Type 1 and Type 2 diabetes mellitus (T2DM), including prevalence, and possible factors eventually increasing LD risk. Search keywords included the following: "Type 1 and Type 2 diabetes mellitus", And insulin-induced Lipohypertrophy, And Lipohypertrophy, And Lipohypotrophy, And HbA1C, And Glycemic variability, And Complications, And Hypoglycemia, And Costs.

The inclusion criteria for this article review were publications in English only on insulin-induced LD in subjects with T1DM and T2DM concerning methodology, epidemiology, pharmacokinetics, prevalence, trends, gender, BMI, insulin injection, injection site rotation, needle size, needle reuse, glycemic control, diabetes duration, comorbidity, and education. We excluded all articles with publication dates before 2010, health-related topics not listed in the inclusion criteria, and all other forms of LD from the search.

The result of this analysis refers to data only derived from previous publications. Therefore no new databases were generated, nor was it necessary to request informed consent from patients. Therefore, already consolidated evidence was used to build a unifying "fil rouge," descriptive of the complete information available on the subject of (IILH)

3. Results

As per inclusion criteria, we selected 14 trials summarized in Tab 1.

Table 1 Research articles published after 2010 listed in order of citation within the text: reference, year of publication, type and number of subjects studied, type of study, topic and objectives

| REFERENCE (n.) | YEAR | SUBJETS (n.) | SUBJECT CATEGORY | TYPE OF STUDY TOPIC | OBJECTIVES |
|----------------|------|----------------|--|---|--|
| 3 | 2019 | 371 | Insulin requiring patients on dialysis | Research Article Case series Epidemiology Methodology | IILH, GV, HYPO frequency and related factors |
| 7 | 2016 | 265 4+4 | T1DM HCPs | Research Article Methodology Epidemiology | how to identify IILH prevalence of IILH in the literature |
| 8 | 2016 | 60 4+4 | Insulin requiring patients HCPs | Research Article Methodology | how to search for IILH role of HCPs experience |
| 11 | 2020 | 718 | T1DM +T2DM | Research Article Open, multicenter, randomized, case-control study | Regional Epidemiology of IILH and related factors |

| | | | | | |
|----|------|------|-------------|---|---|
| | | | | Epidemiology | |
| 12 | 2022 | T2DM | 1160 | Research article Multicenter, observational study Epidemiology Education | To investigate upon training modalities on correct insulin injection techniques and knowledge persistence |
| 14 | 2011 | 180 | T1DM + T2DM | Research Article Methodology Epidemiology | Prevalence of IILH Pharmacokinetics of rapid analogues injected into IILH |
| 15 | 2021 | T2DM | 79 + 79 | Research article Two-arm, open-label, multicenter, randomized, case-control study Education | Durability of structured education on injection techniques |
| 16 | 2018 | 168 | T1DM | Research Article Case-control series Costs | HYPO-related cost saving through structured education |
| 17 | 2022 | T2DM | 319 + 319 | Research article Two-arm, open-label, multicenter, randomized, 18-month case-control study Education Costs | Economic burden of IILH-related HYPOs before and after structured educational training |
| 18 | 2016 | 387 | T1DM + T2DM | Research Article Case-control series Observational | Predictive role of IILH for HYPOS, GV IILH and diabetes-related complications |
| 20 | 2021 | 4499 | T2DM | Research article Randomized, two-arm, open-label, multicenter, case-control intervention study Education CV-Risk | Evaluation of CV-Risk and metabolic consequences of IILH |
| 48 | 2020 | 318 | T2DM | Research Article Open, multicenter, randomized, case-control study Education | Role of intensive structured education on IILH and associated complications |

| | | | | | |
|----|------|-----|-------------|---|---|
| 49 | 2021 | 780 | T1DM + T2DM | Research article Cross-sectional, observational, multicenter, clinical study Skin local complications | To investigate upon IILH-related factors including bruising |
| 50 | 2021 | 100 | T2DM | Research article Open, case-control observational study Clinical Complications | To investigate upon IILH-related microvascular skin changes |

IILH = Insulin-Induced Lipohypertrophy; HCPs = Healthcare Professionals; HYPOs = hypoglycemic episodes; GV = Glycemic variability; CV-Risk = Cardio-Vascular Risk; IT = Injection Technique.

3.1. IILH Prevalence

Very variable IILH frequencies, i.e., 1.7% to 67% (1, 7, 8) are reported in the literature in children and adults. The possible explanation is that the published series often combine patients with T1DM and T2DM, different age ranges, insulin treatment durations, daily injection rates, injection systems (syringes, pens, CSII), and needle lengths and reuse rates (11). However, the most relevant factor consists of the IILH search methodology: in greater detail, the papers most often fail to report curricular qualification and clinical experience in the field of nurses, educators, GPs, endocrinologists, dermatologists, and other very different professionals involved (7,8,11.). Indeed, the diagnostic competence of many healthcare providers is doubtful, as documented by various surveys on knowledge, attitude, and experience carried out in various countries (35, 38). Moreover, data collection methods also suffer from methodological errors. Patient-completed questionnaires are different from systematic and structured IILH searches by expert and trained personnel (10.). It is widely agreed that ultrasonography is the best scientific reference method for IILH identification (39-41). However, requiring expert personnel and being time-consuming and costly, it is more suitable for research than for clinical routine and mass screening (11).

3.2. IILH effect on insulin release

By its structure - hypovascularized, rich in fibrin, made up of two populations of micro- and macro-adipocytes, almost always devoid of external capsule and inflammatory cells, and disrupting the thin layer between subcutis and subcutaneous muscles – IILH may release pen- and pump-injected insulin asynchronously to meals (in the case of fast-acting preparations), and irregularly/unpredictably (as for fast-acting and basal insulins) (22.). IILH nodules can even trap insulin inside, acting as an insulin reservoir, as documented by ultrasonography (39), and as reported by our group in one case of two large colliquated IILH nodules containing 13 times higher insulin concentration than blood (22,43). Conversely, long needles such as those mounted on syringes (mostly 12.7 mm) may unexpectedly get into the richly vascularized muscle lying below the subcutaneous tissue, thus causing severe hypoglycemia due to massive insulin release into the bloodstream (9). Indeed, IILH nodules can modify insulin release-dependent pharmacokinetics, as documented with both multiple daily injection schedules (14) and CSII (42). They associate with high glycemic variability (GV) (11), frequent unexplained hypoglycemic events (Hypos) (18), poor glycemic control (PGC) (11,33), and eventually chronic diabetes complications (33.) which represent consequences rather than causal factors of IILH (11,32). Fortunately, IILH lesions are reversible with adequate and repeated structured education on correct injection techniques (15-17).

3.3. Insulin injection-related discomfort

If it is true that children have a higher pain threshold for insulin injections (1) and still have IILH with a high frequency due to incorrect insulin injection sites rotating, it is difficult to understand why they so often inject insulin into IILH nodules. In reality, it should be considered that, by going into nodules, patients unwillingly or deliberately choose abnormal and avascular areas denervated by multiple injection-related microtraumas aggravated by blunt reused needles with microscopic curls on top (31,33,34).

3.4. Education

At present, therapeutic education (TE) on correct injection techniques remains the most effective weapon to counteract the formation of IILH and to reverse those already formed (15-17). There is no doubt about its effectiveness for short

periods (15, 44, 45, 48) and its ability to reduce the costs of acute complications (16,17), however, there is little evidence on the efficacy of TE in the long term. Such consideration highlights that continuous education through repeated reminder courses is necessary for the efficacy durability, and maintenance of correct injection techniques (17). Furthermore, the effect of a correct injection technique allows an estimated 20 to 30% reduction in insulin doses (16, 17, 46), which contributes to a reduction in insulin costs (11, 17, 46).

3.5. Treatment

In the past, it has been proposed to inject small doses of glucocorticoids with insulin to reduce LH. However, those studies date back to the 90s, when insulin preparations were less purified or composed of insulin polymers staying within tissues longer than current monomeric preparations (1, 29, 31). Various factors stand against this treatment option: (i) no more data has been published in the last decade on glucocorticoid administration with insulin; (ii) the absence of inflammatory cells in IILH documented by histological and electron microscopy-based studies (47-50).

Even liposuction or surgery, previously proposed and advertised on commercial online sites, still needs to be reflected in scientific evidence. Moreover, they cannot represent elective mass therapy. However, they should be considered a technique indicated only in selected cases of particularly voluminous and unsightly IILH (22). In most cases, avoiding the sting for IILH persistence and size duration is enough (15,22). The use of emollient creams with boasted IILH protective effect does not find scientific evidence (32), and, if anything, can even be mechanically dangerous when associated with a massage of lipohypertrophic areas, for the "squeezing" of possible insulin reservoirs with the consequent risk of release into the circulation of significant amounts of insulin and consequent severe hypoglycemia (21).

4. Conclusion

From all this we can deduce the extreme urgency and relevance of spreading a real awareness of how important it is to:

- inject insulin correctly with an appropriate technique;
- correctly search for IILH in the injection sites;
- understand the clinical implications of IILH;
- teach patients the importance of avoiding ILH formation and try to avoid injecting insulin into them;
- stimulate all healthcare providers to consider more carefully the way patients inject insulin, performing periodic IILH assessment with appropriate methodology;
- periodically monitor patients' progress in knowing, knowing how to do, and knowing how to be in terms of insulin injection;
- promote all possible actions at the curricular and extra-curricular level of all healthcare providers involved in insulin therapy to improve knowledge, attitudes and skills on correct injection techniques,
- raise awareness among insulin producers and regulatory bodies so that instructions, cartoons, films and anything else useful for correct injection techniques are always present in all packages and in all the technical and informative material relating to the insulin packages.

Unmet Needs

Although today we have consolidated evidence on risk factors, causes, and consequences of IILH and the value of education for their prevention and treatment. some aspects remain unresolved, such as the possibility that substantial differences exist between T1DM and T2DM in epidemiological and pathophysiological kinds, linked to various factors still under study. Another point requiring further investigation concerns the possibility that different devices, such as syringes and infusion sets for insulin pumps and pens, have different IILH-inducing potentials. At the same time, little or nothing is known about the effect of jet-administering insulin without a needle. Finally, a further neglected topic concerns the subcutaneous injection of other non-insulin drugs, such as Glucagon-Like Peptide-1 Receptor Agonists, with or without the addition of basal insulin. On all these topics, it will be necessary to plan specific studies.

Compliance with ethical standards

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All authors declare no conflicts of interest related to this paper.

Statement of ethical approval

Our text contains no personal new data and merely refers to previous scientific articles. The Authors act according to standard ethical editorial rules.

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Authors' contribution

SG, ES, LB, and FS thought of and wrote this text, and shared it jointly.

Data Availability Statement

Data is contained within the article.

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