


Commentary

# Insulin Injection-Related Skin Lipodystrophies: Blemish or Pathology?

Felice Strollo <sup>1</sup>, Ersilia Satta <sup>2</sup> and Sandro Gentile <sup>2,3,\*</sup> <sup>1</sup> Endocrinology and Diabetes, IRCCS San Raffaele Pisana, I-00163 Rome, Italy<sup>2</sup> Nefrocenter Research & Nyx Start-Up, I-80030 Naples, Italy<sup>3</sup> Department of Internal Medicine, Luigi Vanvitelli University of Campania, I-50138 Naples, Italy

\* Correspondence: s.gentile1949@gmail.com

**Abstract:** The number of adult individuals with insulin-treated diabetes mellitus (DM) is steadily increasing worldwide. The main local complications of insulin injection are lipohypertrophies (LHs), i.e., subcutaneous nodules consisting of aggregates of macro-adipocytes and fibrin. These nodules result from errors repeatedly made by patients while injecting insulin. Despite being very common, LH lesions/nodules due to incorrect insulin injection techniques are often flat and hardly visible and thus require thorough deep palpation examination and ultrasonography (US) for detection. Identifying LHs is crucial, especially in elderly and frail subjects, because they may eventually result in poor diabetes control due to associated unpredictable insulin release patterns. Raising awareness of the adequate detection of LHs and their clinical consequences is crucial and urgent. A call to action is required on this topic at all levels of undergraduate and postgraduate education.

**Keywords:** diabetes; insulin; injection technique; lipohypertrophy



**Citation:** Strollo, F.; Satta, E.; Gentile, S. Insulin Injection-Related Skin Lipodystrophies: Blemish or Pathology? *Diabetology* **2022**, *3*, 615–619. <https://doi.org/10.3390/diabetology3040047>

Academic Editor: Peter Clifton

Received: 2 November 2022

Accepted: 29 November 2022

Published: 1 December 2022

**Publisher's Note:** MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.



**Copyright:** © 2022 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

## 1. Introduction

Lipohypertrophy (LH) at insulin injection sites is a typical complication in insulin-requiring type 2-diabetic people resulting from the localized accumulation of subcutaneous fat [1,2]. Unfortunately, it occurs frequently, affecting 47% (range 5–70%) of patients on insulin [1,3]. However, LH can be prevented by overcoming severe educational defects that cause the patient to progressively acquire bad injection habits, including the choice of restricted skin areas, the repeated utilization of a single needle, or ice-cold preparations.

## 2. What May Happen to People with LHs

LHs do not only represent skin imperfections. Indeed, they often have severe metabolic consequences due to scattering insulin absorption and, inevitably, high blood glucose oscillations [4,5]. A few years ago, we published the case of a woman who had a prominent LH on her abdomen and, wishing to wear a bikini, steadily and vigorously massaged her unsightly abdominal lump with the most disparate cosmetic creams. As a result, she woke up in the emergency room of a hospital after a severe hypoglycemic event—which she did not remember—caused by the sudden release of the insulin trapped in the LH nodule [6].

## 3. A Case of Monster LH

In another case, we described the presence of two abdominal tangerine-like symmetrical bumps with a central hyperchromic navel, which, on ultrasound examination, turned out to be LHs with a gelatinous/fluid content. When analyzed, the latter had a 13 times higher insulin concentration than in the blood. These lesions only disappeared after three years of correct injection behavior and regularly occurring educational training. However, despite the size of the scarring umbilications having decreased, the dyschromia still subsided [7] (see Figure 1).



**Figure 1.** Two major LH swellings were evident at the two sides of the navel markedly protruding from the cutaneous plane (**left** panel). The central areas of both LH lesions were easily identified by sight and touch as umbilicated, hyperchromic, and clefted. In the (**right** panel), ultrasound scans of lipo-hypertrophic area are also provided: the thickening of the dermis is clearly visible together with the central, colliquative area.

#### 4. Practical Considerations

Why do patients stubbornly inject insulin into lipodystrophic nodules? The answer is complex and largely depends on educational deficiencies when starting insulin therapy, which are aggravated by the lack of required periodic injection site inspections by diabetes teams, as previously described by our team in [7]. However, another reason behind it is the painlessness of mistreated and thus denervated skin tissue hosting LHs. Indeed, about half of patients on insulin self-injecting the drug four times a day, i.e., 1460 times per year, unconsciously or secretly accept risking high blood sugar levels by avoiding frequent painful injections [8].

#### 5. Why Do People with Diabetes Forget the Lessons over Time?

The answer is not simple, but one can resort to a fundamental principle of therapeutic education, borrowing the axiom “knowing is not the same thing as knowing how to do”. Evidence for this stems from a Charlie Brown strip where the famous cartoon character—drawn by Charles Monroe Schulz in the 1950s—informed Lucy of having taught Snoopy to whistle. When she objected that Snoopy could not whistle yet, he retorted that he had only said he had taught him, not that Snoopy had learned! In addition to this, we cannot rule out the role for comfortable movements, especially for older adults with joint difficulties, a certain degree of habit, and, for some, the tendency for depression and poor self-care, which are typical traits of chronic diseases with a longstanding asymptomatic phase such as diabetes. Finally, we should remember how difficult it is to change consolidated habits involving errors and bad clinical practice [1,8].

#### 6. What Are the Consequences of Injection Technique Errors?

First, an unpredictable absorption of the preparation injected into the LH alters the expected synchronism between the post-meal rise in blood sugar and the immediate insulin action [4,5]. The direct consequence of such a phenomenon is considerable variability in circulating glucose levels, which is a recognized severe cardiovascular risk factor [9]. Secondly, such variability entails poor glycemic control and, even worse, repeated dangerous hypoglycemic episodes in the absence of eating errors, missed meals, vomiting, diarrhea, and insulin dose calculation errors. The abovementioned LH consequences also burden patients with a poor quality of life and the national health system with excess medical and social expenditure [10]. The skin undergoes fundamental structural changes with aging, potentially increasing the risk for LHs. Therefore, LH side effects are hazardous in elderly individuals because of their inner frailty, frequently associated comorbidities, and possible hypoglycemia-related acute cardiovascular events [11].

When undergoing a severe episode of hypoglycemia, the patient can become unconscious and thus requires the intervention of family members, caregivers, or anyone else making emergency calls to the GP or first-aid services. This event might end in hospitalization, with the patient's and caregiver's absence from the workplace.

The above entails an apparent increase in costs quantifiable through the national tariff for health services and would not occur if adequate educational training was provided [9].

Indeed, our recent data document tenfold higher hypoglycemic event-related costs in patients with LH than without LH, and over eightfold lower costs—therefore, approaching those of patients injecting insulin correctly—after adequate systematic, multimodal, and repeated educational training [7,8,10].

Moreover, when injected into healthy skin instead of LH nodules, required insulin doses decrease by 20–25%. Despite being twenty times lower than those due to less unpredictable hypoglycemic events, the resulting savings are of great value when projected on large populations and compared to the annual costs of insulin, especially in the case of new rapid or basal analogs [1,2,9].

### **7. What Can We Do to Prevent Lipohypertrophies?**

Indeed, the picture is not comforting. Suffice it to say that a recent survey conducted in China and other countries on health professionals (doctors and nurses) mercilessly documents that over 50% of patients have poor knowledge about LHs, associated metabolic consequences, and, even worse, how to avoid or counteract this type of complication [12–18].

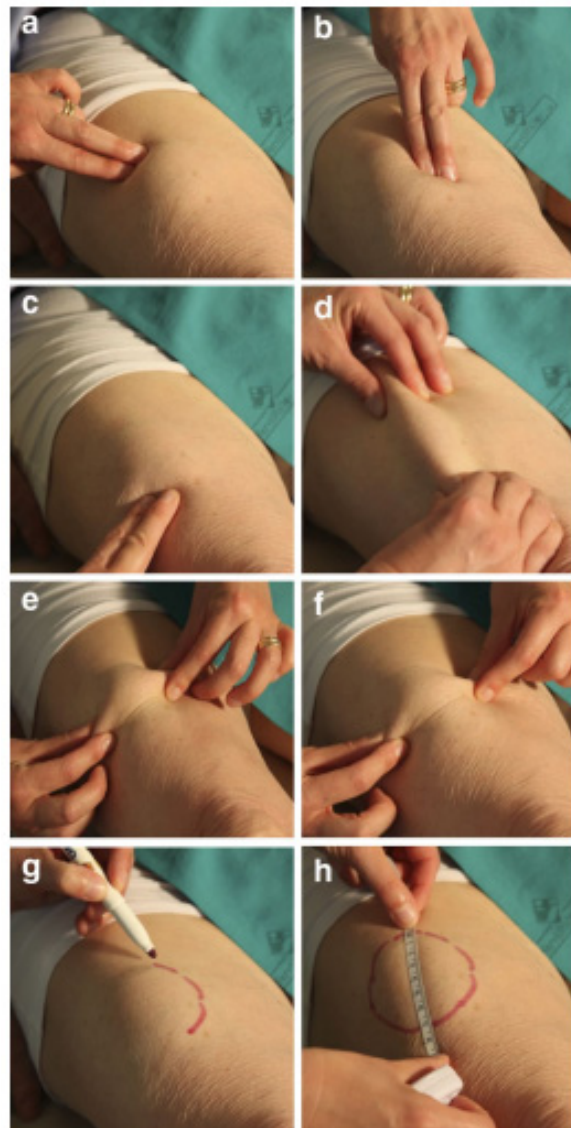
In Italy, the situation is similar. Indeed, the occurrence of LH in at least 45% of insulin patients documents the similar level of our treatment system's inefficiency.

Unfortunately, apart from a few willing people who are stubbornly engaged in therapeutic education, including that involving correct injection techniques, LH is most often forgotten or ignored, thus becoming a “non-problem”.

### **8. A Proposal for the Future**

Considering that three to four million persons in Italy have diabetes, and about 40–50% of them will sooner or later require insulin, correct insulin injection techniques should have a more prominent place in undergraduate, postgraduate, and specialization courses. Specifically, doctors and nurses should follow dedicated training procedures on proper injection techniques. Outpatient general medicine practices and diabetes wards should also become involved in practical education paths, including primarily structured LH identification methods (Figure 2) [3]. In our youthful memories, none of this existed, and it was the experience in the field that sometimes compensated this absence. Another practical solution to the problem may also come from insulin manufacturers, who could include in pens and vial packages dedicated visuals and detailed descriptions on how to inject and use insulin correctly.

The relaxed, even condescending attitude towards LHs has to change, and we count on our most resourceful readers to make this happen as fast as possible.



**Figure 2.** LH identification technique. The figure shows how to identify a lesion after a thorough inspection of the area by performing repeated vertical and horizontal fingertip movements over and around it (a–c), pinching it (d–f), and marking it (g), as well as how to finally measure it (h).

### 9. Key Summary Points

1. Improper Insulin injection causes skin lipohypertrophic lesions (LHs), which are often flat and barely visible, thus requiring thorough deep palpation examination and ultrasonography (US) for identification;
2. The detection of LHs is crucial to prevent poor diabetes control due to unpredictable insulin-release patterns;
3. The skin undergoes fundamental structural changes with aging, potentially increasing the risk of developing LHs;
4. Too many healthcare professionals (doctors and nurses) know little or nothing about lipohypertrophy and its associated metabolic consequences and, worse, they do not know how to avoid or counteract this type of complication;
5. The data from the literature suggest the need (i) to take specific actions to prevent and control the high risk of acute hypoglycemia-related cardiovascular events, especially in older subjects, and (ii) to identify specific, better-targeted, practical, and structured educational programs suited to older patients.

**Author Contributions:** S.G., E.S. and F.S. ideated and wrote this text and shared responsibilities jointly. All authors have read and agreed to the published version of the manuscript.

**Funding:** The authors received no funding for this manuscript.

**Institutional Review Board Statement:** The IRB from the Naples “Vanvitelli” University approved the study on 16 July 2022 under the n. 11619.

**Informed Consent Statement:** Not applicable.

**Data Availability Statement:** Data is contained within the article.

**Conflicts of Interest:** The authors declare no conflict of interest.

## References

- Gentile, S.; Guarino, G.; Della Corte, T.; Marino, G.; Satta, E.; Pasquarella, M.; Romano, C.; Alfrone, C.; Strollo, F. Role of Structured Education in Reducing Lypodistrophy and its Metabolic Complications in Insulin-Treated People with Type 2 Diabetes: A Randomized Multicenter Case–Control Study. *Diabetes Ther.* **2021**, *12*, 1379–1398. [[CrossRef](#)] [[PubMed](#)]
- Blanco, M.; Hernández, M.; Strauss, K.; Amaya, M. Prevalence and risk factors of lipohypertrophy in insulin-injecting patients with diabetes. *Diabetes Metab.* **2013**, *39*, 445–453. [[CrossRef](#)] [[PubMed](#)]
- Gentile, S.; Guarino, G.; Giancaterini, A.; Guida, P.; Strollo, F.; AMD-OSDI Italian Injection Technique Study Group. A suitable palpation technique allows to identify skin lipohypertrophic lesions in insulin-treated people with diabetes. *SpringerPlus* **2016**, *5*, 1–7. [[CrossRef](#)] [[PubMed](#)]
- Gentile, S.; Agrusta, M.; Guarino, G.; Carbone, L.; Cavallaro, V.; Carucci, I.; Strollo, F. Metabolic consequences of incorrect insulin administration techniques in aging subjects with diabetes. *Geol. Rundsch.* **2010**, *48*, 121–125. [[CrossRef](#)] [[PubMed](#)]
- Famulla, S.; Hövelmann, U.; Fischer, A.; Coester, H.-V.; Hermanski, L.; Kaltheuner, M.; Kaltheuner, L.; Heinemann, L.; Heise, T.; Hirsch, L. Insulin Injection Into Lipohypertrophic Tissue: Blunted and More Variable Insulin Absorption and Action and Impaired Postprandial Glucose Control. *Diabetes Care* **2016**, *39*, 1486–1492. [[CrossRef](#)] [[PubMed](#)]
- Improta, M.; Strollo, F.; Gentile, S.; AMD-OSDI Study Group on Injection Technique. Lessons learned from an unusual case of severe hypoglycemia. *Diabetes Metab. Syndr. Clin. Res. Rev.* **2019**, *13*, 1237–1239. [[CrossRef](#)] [[PubMed](#)]
- Gentile, S.; Guarino, G.; Strollo, F. How to treat improper insulin injection-related lipohypertrophy: A 3-year follow-up of a monster case and an update on treatment. *Diabetes Res. Clin. Pract.* **2020**, *171*, 108534. [[CrossRef](#)] [[PubMed](#)]
- Gentile, S.; Guarino, G.; Della Corte, T.; Marino, G.; Satta, E.; Pasquarella, M.; Romano, C.; Alfrone, C.; Giordano, L.; Loiacono, F.; et al. The Durability of an Intensive, Structured Education-Based Rehabilitation Protocol for Best Insulin Injection Practice: The ISTERP-2 Study. *Diabetes Ther.* **2021**, *12*, 2557–2569. [[CrossRef](#)] [[PubMed](#)]
- Nusca, A.; Tuccinardi, D.; Albano, M.; Cavallaro, C.; Ricottini, E.; Manfrini, S.; Pozzilli, P.; Di Sciascio, G. Glycemic variability in the development of cardiovascular complications in diabetes. *Diabetes/Metabolism Res. Rev.* **2018**, *34*, e3047. [[CrossRef](#)] [[PubMed](#)]
- Gentile, S.; Strollo, F. Cost saving effects of a short-term educational intervention entailing lower hypoglycaemic event rates in people with type 1 diabetes and lipo-hypertrophy. *Diabetes Res. Clin. Pr.* **2018**, *143*, 320–321. [[CrossRef](#)] [[PubMed](#)]
- Gentile, S.; Guarino, G.; Della Corte, T.; Marino, G.; Fusco, A.; Corigliano, G.; Colarusso, S.; Piscopo, M.; Improta, M.R.; Corigliano, M.; et al. Lipohypertrophy in Elderly Insulin-Treated Patients With Type 2 Diabetes. *Diabetes Ther.* **2020**, *12*, 107–119. [[CrossRef](#)] [[PubMed](#)]
- Wu, X.; Zhao, F.; Zhang, M.; Yuan, L.; Zheng, Y.; Huang, J.; Li, Y.; Li, C. Insulin Injection Knowledge, Attitudes, and Practices of Nurses in China: A Cross-Sectional Nationwide Study. *Diabetes Ther.* **2021**, *12*, 2451–2469. [[CrossRef](#)] [[PubMed](#)]
- Adhikari, S.; Poudel, R.S.; Rajbanshi, L.; Shrestha, S. Assessment of Insulin Injection Practice of Nurses Working in a Tertiary Healthcare Center of Nepal. *Nurs. Res. Pract.* **2018**, *2018*, 1–6. [[CrossRef](#)] [[PubMed](#)]
- Mushta, A.M. Study of insulin injection technique amongst the nursing staff. *Pak. J. Med. Sci.* **2006**, *22*, 310–312.
- Yacoub, M.; Demeh, W.; Darawad, M.; Barr, J.; Saleh, A.; Saleh, M. An assessment of diabetes-related knowledge among registered nurses working in hospitals in Jordan. *Int. Nurs. Rev.* **2014**, *61*, 255–262. [[CrossRef](#)] [[PubMed](#)]
- Theofanidis, D. In-Hospital Administration of Insulin by Nurses in Northern Greece: An Observational Study. *Diabetes Spectr.* **2017**, *30*, 175–181. [[CrossRef](#)] [[PubMed](#)]
- Robb, A.; Reid, B.; A Laird, E. Insulin knowledge and practice: A survey of district nurses in Northern Ireland. *Br. J. Community Nurs.* **2017**, *22*, 138–145. [[CrossRef](#)] [[PubMed](#)]
- Derr, R.L.; Sivanandy, M.S.; Bronich-Hall, L.; Rodriguez, A. Insulin-related knowledge among health care professionals in inter-nal medicine. *Diabetes Spectr.* **2007**, *20*, 177–185. [[CrossRef](#)]