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*Opinion*

# Lipodystrophies from Insulin Injection: An Update of the Italian Consensus Statement of AMD-OSDI Study Group on Injection Technique

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**Abstract:** The causes and metabolic consequences of lipohypertrophy (LH) from incorrect insulin injection techniques have been well-known for a long time and are the subject of countless publications. However, only some researchers propose structured research modalities for LH and programs to teach patients how to prevent them and minimize their effects, thus contributing to complete rehabilitation. Experts and scientific societies have produced consensus documents and recommendations to spread the culture of LH and its complications among clinicians. However, they should go deeper into LH detection methods. This short article analyzes the recent literature on the best way to explore and find more or less evident LH lesions by using a structured and validated clinical methodology to benefit the many clinicians without access to technological equipment such as ultrasonography. This text also aims to bring awareness that since the last published recommendations on injection techniques, new needles for insulin injection, more technologically advanced and suitable for specific populations, have come to market but still need a thorough evaluation.

**Keywords:** diabetes; insulin; lipodystrophy; injection technique; clinical detection; recommendations; rehabilitation

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## 1. Introduction

From the onset of insulin in the last century, it was immediately apparent that the daily injections necessary to administer it involved local skin complications such as subcutaneous lipoatrophy (LA) [1] due to impurities of the first insulin preparations and to related immune-allergic reactions [2]. Today, technology makes it possible to inject extremely pure insulin preparations without the devastating atrophying effects of the early insulin era. However, today, a further variant of insulin injection lipodystrophy (LD), the skin lipohypertrophy (LH), is present in numerous patients on multi-injection therapy [3]. From a purely descriptive point of view, therefore, with the term "lipodystrophies" we mean both forms of skin atrophy (LA) and hypertrophy (LH). The former lesions are now rare and represent less than 5% of all LDs. At the same time, the latter is much more frequent, being the main local complication of insulin injections [2]. LH is due to the anabolic action of insulin and in addition to the systematic puncture of narrow areas of the skin (usually an extension comparable with that of a credit card), reusing the same needle several times, injecting cold insulin, and using too long and thick needles [2,4,5].

The phenomenon of LH due to incorrect injection technique is well-present in the literature. Its diffusion concerns just under 50% of all subjects in multi-injection therapy

with insulin [6–8], but with wide variations in frequency, linked to the research method, too often approximate, and the lack of healthcare provider experience or structured identification method [9–12]. In reality, this is a gap in scientific research. Indeed, when going through leading literature banks (e.g., Scopus and PubMed), we find numerous scientific articles describing case histories with and without LH and clinical cases of subjects with LD without giving due relevance to the identification method [13,14]. A sure cornerstone of literature concerns the comparison between manual and ultrasound research of LH, which undoubtedly decrees the diagnostic superiority of ultrasonography over manual [15]. However, due to the high number of patients self-injecting insulin, the equipment and dedicated personnel costs, and the time required for each examination, ultrasonography remains confined to the scientific field. Indeed, ultrasonography is unsuitable for widespread clinical use, especially in specific care settings such as outpatients or economically disadvantaged and developing countries [16]. Nevertheless, some handy yet evidence-based methodological indications at the clinical level may be helpful (Table 1) [13,14,16–18].

**Table 1.** Methodological indications on how to manually search for skin LH.

| | **CORRECT LH SEARCH SEQUENCE** |
|---|---|
| 1 | Have the patient indicate all skin areas where he or she injects the insulin and examine all of them |
| 2 | Conduct the exam in a well-lit environment, preferably with natural light |
| 3 | Examine the patient supine without clothing and then in a standing position |
| 4 | Rotate the standing patient to take advantage of the incidence of light bringing out LH profile and elevation |
| 5 | Ask the patient to get muscles relaxed during the examination |
| 6 | Perform superficial palpation of the injection sites, passing the examining hand over and over again, looking for nodules or pasty areas of greater consistency than the surrounding skin |
| 7 | Repeat the palpation as described above, with more force to sense any deeper LH |
| 8 | Perform the pinching maneuver, taking a flap of skin between the index finger and thumb, to evaluate the thickness of the skin fold and compare it with nearby areas that are not affected by the injections: the LH is recognizable by a greater thickness of the fold |
| 9 | The set of previous findings allows us to describe an area of skin containing an LH |
| 10 | The LHs can be small or several centimeters large, protruding on the skin or flat; their recognition by sight alone risks not identify clear palpable LHs |
| 11 | Show identified LHs to the patient, explain why they form, what metabolic consequences they entail, and why the need to correctly perform the insulin injection |
| 12 | Give precise and motivated indications on how to correctly inject insulin (injection site rotation, no reuse of the same needle, insulin at room temperature, use of short and thin needles as recommended) |
| 13 | Skin examination (e.g., acanthosis nigricans, insulin injection or insertion sites, lipodystrophy) is a component of the comprehensive diabetes medical evaluation at initial and annual visits, besides every follow-up |

If errors in insulin injection technique cause LH, recommendations on correct injection techniques are critical for current treatment and rehabilitation in case of marked LH-related glucose variability. In Italy, an intercompany study group of AMD (Italian Medical Association of Diabetologists) and OSDI (Italian Association of Nurses on Diabetes) [19] published recommendations on optimal insulin injection techniques in 2016, and similar recommendations were published shortly after, resulting from the conclusions of an international meeting of a panel of experts from 52 countries, held in Rome in 2015 [20].

Those conclusions are substantially similar and confirm the need for:

1. A preventive search for LH to avoid injecting insulin into them;
2. Constant injection site rotation ensuring a distance of at least 1 cm between two successive injections and utilization of the entire surface of injection areas identified

in the abdomen, external and rear sides of the arms, upper external side of the thighs and buttocks;
3. Single use of each pen needle (1 needle = 1 injection);
4. Choice of 32 G × 4 mm needles even in overweight and obese subjects;
5. Proper insulin storage;
6. Ice-cold insulin avoidance;
7. No skin massage after the injection;
8. No injection through clothing;
9. Thorough hand and skin hygiene;
10. No pinch maneuver or acute angle needle inclination at the time of injection.

In 2017, the Italian AMD-OSDI study group updated the recommendations on injection techniques, also considering pregnant women and insulin pump (CSII) users. Their document suggested lateral areas of the abdomen in the first months and advised against using the whole abdominal area in the following months in pregnant women. For CSII users, it recommended an effective needle insertion site rotation and the choice of needles guided by the specialist care team [21]. ADA Standards of Medical Care in Diabetes—2022 accurately echoed the conclusions of such documents [17]. In particular, this document refers to the 2016 recommendations [20] and suggests skin examination as an inescapable component of the comprehensive diabetes medical evaluation at initial, follow-up, and annual visits. Furthermore, the ADA document considers the 4 mm and 32 G needles proposed in the 2016 document as the reference needle for obese subjects in the absence of evidence for subsequent shorter and thinner needles.

Indeed, 4 mm/33 G and 3.5 mm/34 G needles came to the market after the 2016 consensus was published. Two studies evaluated small cohorts of insulin-treated subjects for their non-inferiority to 4 mm/33 G and 3.5 mm/34 G in terms of (i) patient satisfaction, (ii) pain sensation at treatment start, (iii) bruising, (iv) insulin leakage, (v) variations in fructosamine, and (vi) fasting and post-meal glucose levels [22,23]. In essence, the effects of the two needle types are substantially overlapping, with only a slightly increased effort perceived by patients at pressing the button that is used to have insulin flowing through the needle due to reduced gauge (G). ADA experts did not consider these papers, probably due to the few cases they examined. However, 3.5 mm needles could be helpful in selected populations. The latter might include young children, skinny adults, pregnant women, and hemodialyzed subjects who are often malnourished and underweight and quickly develop LH [24]. These subjects could successfully use ultra-short needles to avoid the risk of intramuscular injections related to their ultra-thin subcutaneous adipose tissue.

However, using excessively thin needles requires an extra effort to press the pen button when injecting insulin, thus eventually causing trouble to older people with hand problems. Indeed, the elderly's hands are often home to arthrosis, arthritis, carpal tunnel syndrome, or, especially in North-European men, thickening of the palmar aponeurosis (Dupuytren's disease). Such abnormalities are easily diagnosed through an accurate physical examination and by asking the patient to write down a short sentence or to perform the tabletop test (i.e., placing fingers flat on a table). They prevent patients from pressing the pen button long enough to complete the full insulin dose injection and keep it pressed ten more seconds after that, as expected to avoid any drug leakage.

A further, too often disregarded issue is the need to add details in electronic medical records concerning LH presence, site, size, texture, and degree of projection on the skin surface, if so ever. Such a habit could let patients and healthcare providers follow up on LH changes and monitor the effectiveness of educational efforts over time by comparing progressive lesion improvement with metabolic parameters, including glucose time-in-range and variability, which are well-known risk factors for chronic diabetes complications worsening (Figure 1 and Table 2).

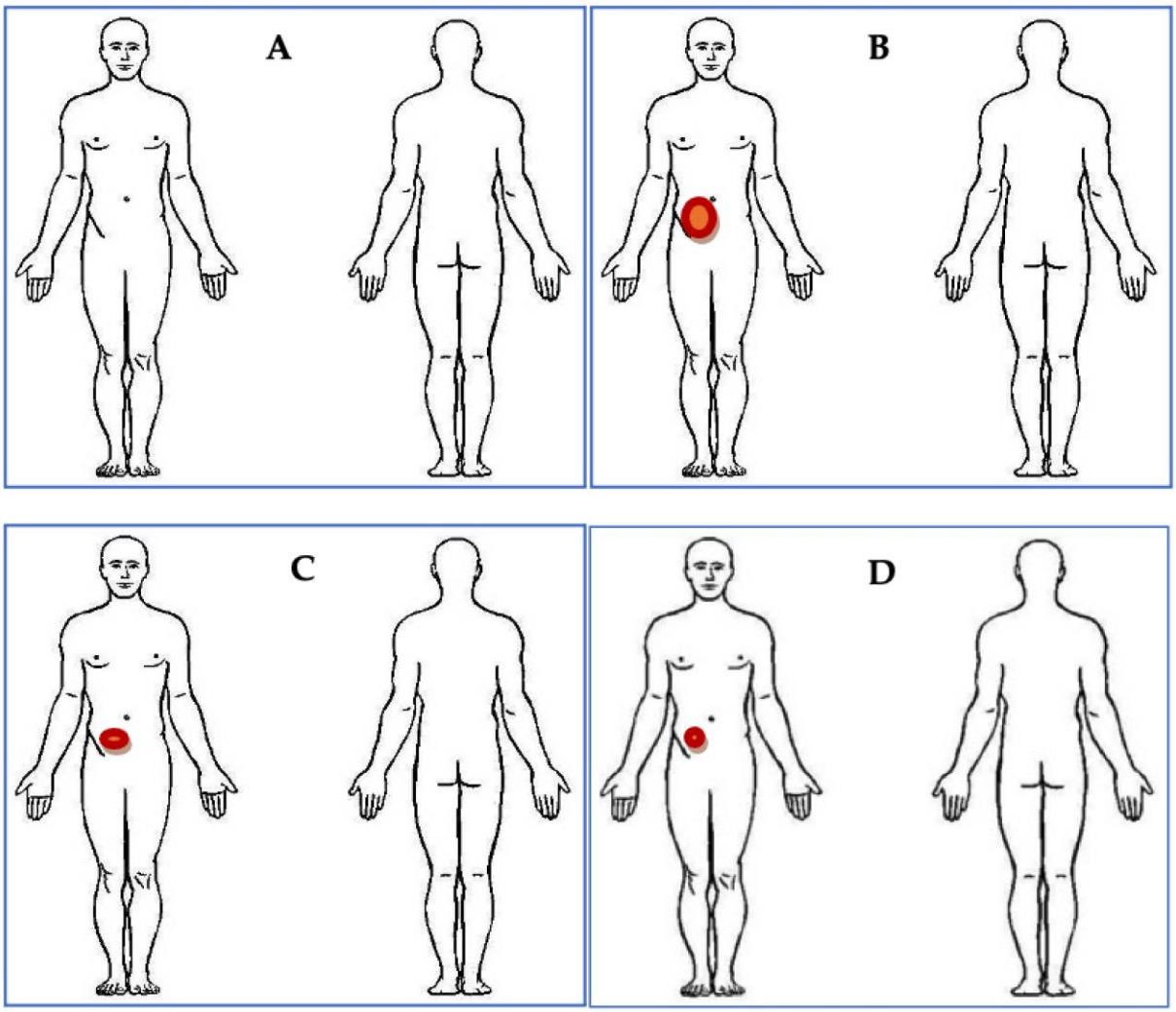


**Figure 1.** Body image suitable for LH site and size recording over time. Panel (**A**): no LH is present. Panel (**B**): a large abdominal LH is present. Panels (**C**,**D**): the LH size progressively decreases during follow-up.

**Table 2.** LH features recording grid. Tick the box accordingly.

| LH Features | Right Arm | Left Arm | Right Thigh | Left Thigh | Right Hemi-Abdomen | Left Hemi-Abdomen | Right Buttock | Left Buttock |
|---|---|---|---|---|---|---|---|---|
| **Present** | | | | | | | | |
| **>4 cm** | | | | | | | | |
| **<4 cm** | | | | | | | | |
| **Protruding** | | | | | | | | |
| **Flat** | | | | | | | | |
| **Hard-elastic** | | | | | | | | |
| **Soft** | | | | | | | | |

Another handy and practical tool allowing the clinician to efficiently monitor lesions could be a digital checklist of actions to be taken for LH detection and follow-up. It should be included in each patient's medical record with a popup alert periodically encouraging the clinician to verify injection site conditions. A similar recording method could also help take note of educational activities performed and the patient's ability to accordingly act. For instance, healthcare providers should preliminarily check whether or not an individual patient can perpendicularly insert the needle in the pen so that the inner side

of the needle does not bend and correctly penetrates the insulin reservoir rubber cap, which is a prerequisite for easy and reliable fluid flow into the skin at the time of injection.

Diabetes-related clinical records should include a detailed checklist devoted to all actions needed to identify LH in insulin-treated patients, as follows:

- Are you sure the explanations you gave to your patient when prescribing insulin were exhaustive and sufficiently clear to let him/her understand how to correctly perform injections?
- Did you explain to him/her how the insulin pen works?
- Did you show him/her how to insert the needle on top of the pen?
- Did you show him/her how to hold the pen at the time of injection?
- Did you provide him/her a chart or cartoon displaying clear indications of the best injection site selection?
- Did you give him/her clear information concerning the importance of selecting the correct needle length and inserting it onto the skin surface at a correct angle?
- Did you tell him/her how to store insulin and avoid ice-cold insulin injections?
- Did you tell him/her that too long needles pose him/her a risk of reaching the muscle tissue below the subcutaneous layer in the case of thin areas, and intramuscular injections make insulin absorption faster, thus often causing unexpected hypoglycemia?
- Did you take enough time to show him/her the best way to perform injection site rotation within separate skin areas?
- Did you explain to him/her the appropriate distance to keep among injection sites?
- Did you stress the importance of pressing the pen button for at least 10 s before taking the pen out of the skin enough?
- Did you repeatedly mention that disposable needles are to be used only once and then discarded?
- Did you remind him/her that, when repeatedly using the same injection site, he/she might give rise to skin nodules causing insulin absorption abnormalities with consequent large blood glucose variability, poor diabetes control, and ever-increasing insulin?
- Did you explain to him/her, especially when insulin-treated for a long time, that it is necessary to self-palpate the skin area in search of nodules and to avoid them if present?
- Did you make sure that, besides understanding all the information pills provided, he/she has taken the habit of correctly putting into practice the teachings you have told and shown so far?

It is easy to check all the abovementioned education elements by simply asking the patient to perform one or more injections in the presence of the diabetes team members and correct any errors in execution.

All insulin-treated subjects should undergo education sessions, including extensive retraining, regularly and at least annually [4,8,18], without forgetting to verify acquired habits in terms of the correct sequence of actions required to appropriately handle, store, and inject insulin.

Indeed, only regularly occurring meetings meant to verify the correct sequence of insulin injection-related actions may yield reliable long-term therapeutic results, thus preventing the worthlessness of the relentless ongoing technological advances in pen and needle engineering and progress in pharmacology/biotechnology in pursuit of progressively more "physiologic" and pure insulin preparations. All the above reflect practical economic considerations but are also better for health and are especially meant to improve the patient's quality of life as much as possible. Indeed, a steadily correct injection habit not only avoids the ever-increasing costs of insulin spoiled by intranodular trapping but also improves glucose control and dramatically reduces hypoglycemic events [4,8,18]. Our daily experience has been supported by experimental data so far. It

provides us with a solid motivation to go on with what initially was a vast educational effort and gradually became routine. Indeed, now we feel fully rewarded by our patient's satisfaction with his/her easily perceived better quality of life. Should such a miracle happen, insulin-treated subjects would no more exchange their serene awareness of a present free of sudden, unexpected, and frightening hypoglycemic events and a future free of complications with a painless injection performed into an almost insensitive, denervated lipodystrophic nodule.

At present, while waiting for such a dream to come true in most diabetes wards worldwide, it is of utmost importance that healthcare teams verify that patients perform self-palpation efficiently enough to detect LHs and, after that, always choose healthy skin sites when injecting the drug, considering the possible "unintentional" choice of painless lesioned areas.

In conclusion, we underline the need for (i) a more careful, systematic, and structured search for cutaneous LH related to injection technique errors; (ii) care teams systematically searching for LH and teaching patients how to recognize and avoid LH while injecting insulin; (iii) updated guidelines and recommendations on correct injection techniques in the light of recent advances in insulin needle technology; and (iv) education of patients ignoring those documents and only trying to avoid discomfort at the time of injection [25,26]. Given the unstoppable growth of the population with diabetes—also due to the increase in the number of post-COVID-19 cases [27]—all what mentioned above is necessary and urgent to prevent the most potent available drug from being nullified and to avoid chronic diabetes complications by improving treatment effectiveness in people on multiple injection regimens. One hundred years have passed since the introduction of insulin into therapy, and some questions spontaneously arise: will all this be enough? Will it take another 100 years to solve the problems of insulin-induced LH [28]?

Finally, an additional interesting element to consider is the LH-inducing potential of non-insulin-containing anti-hyperglycemic drug preparations, if so ever. Indeed, such a theme deserves attention, in our view, because no investigators systematically explored it so far, and, what is even more intriguing, such injections would lack insulin's anabolic effects, which have been listed for years among typical LH contributing factors. To the best of our knowledge, only one paper related to that issue was published by our group some years ago, dealing with a formulation containing a once-weekly long-acting exenatide, i.e., a glucagon-like peptide-1 receptor agonist (GLP-1RA), repeatedly injected into the same skin site, as reflected by Figure 2 **[**29**]**.

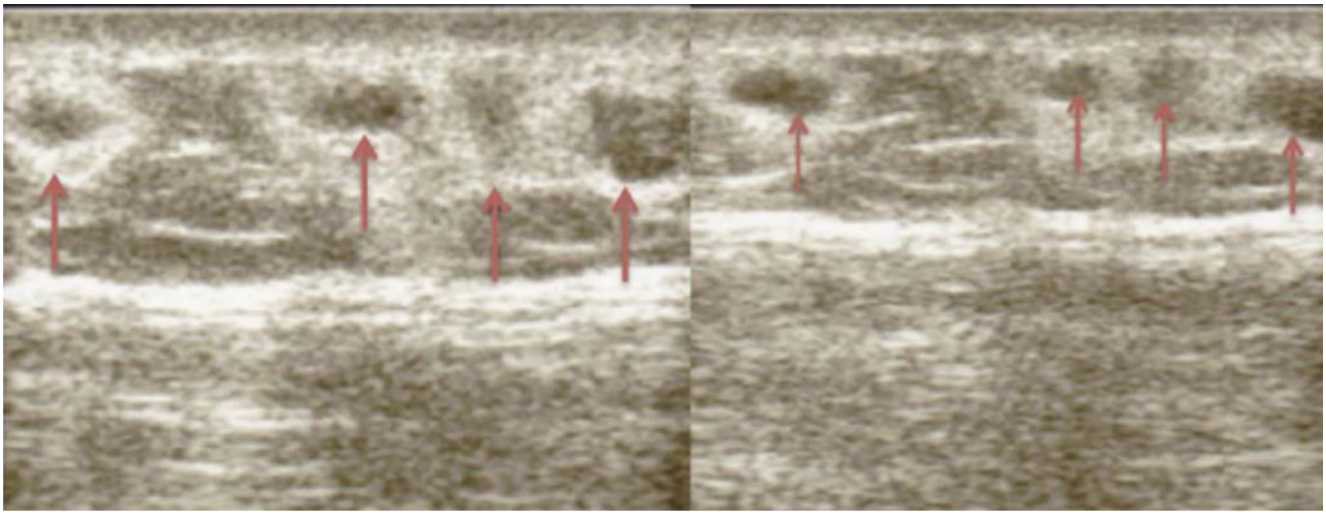

**Figure 2.** Ultrasound image of multiple nodules found 8 weeks after repeated subcutaneous injections. Formulation performed within a small skin area within the arm. Nodules displayed hypoechoic patterns with hyperechoic borders (29, modified).

Possible LH-inducing effects of mixed basal insulin-GLP-1RAs also warrant investigation. Therefore, the scientific community is responsible for fostering awareness of the negative long-term consequences of careless injection habits to improve knowledge in the field and perform adequate, effective prevention and treatment measures.

## 2. Summary Points

1. Lipohypertrophy (LH) due to incorrect injection technique is widespread, underdiagnosed, and mainly ignored by clinicians.
2. We have national and international recommendations on correct injection techniques, but LH is, nevertheless, ubiquitous.
3. A call to action is needed to implement the culture of LH and its complications.
4. Recommendations must take into account advances in technology, and new research is needed to prove the usefulness of the new devices.
5. It is necessary to implement structured clinical diagnostic paths for the identification of LH, especially in care settings without ultrasonography, an unsuitable and expensive method for population and screening studies.

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