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Review

A Neglected Complication of Insulin Therapy Due to Errors in Injection Technique: Skin Lipohypertrophies: A Narrative Review

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Abstract: Over 100 years after its commercialization, the insulin administration method still needs elementary education. Such observation contrasts with technological progress constantly elaborating new (e.g., weekly) insulin preparations, capable of mimicking the pharmacokinetics of insulin produced by the human pancreas and exploring alternatives to injection. However, insulin administration remains anchored to the subcutaneous route, thus creating the conditions for lipohypertrophies (LHs), a still too frequent and ubiquitously widespread skin complication that, despite being avoidable with an adequate educational path, affects up to 60% of patients and even more. Considering that there are approximately 580 million adult diabetic people in the world today, at least half of whom (290 million) self-inject insulin, should 50% of the latter have LH, approximately 145 million people and even more? Considering that there are approximately 580 million adult diabetic people in the world today, at least half of whom (290 million) self-inject insulin, should 50% of the latter have LH, approximately 145 million people would suffer from such a complication, thus causing a severe problem for the global health system. Indeed, besides being unsightly, LHs cause poor glycemic control, large glucose variability, and frequent unexplained hypoglycemia, and display a strong correlation with micro- and macrovascular complications, inevitably worsening the quality of life of diabetic people. In this narrative review, after a brief description of the alternative routes of administration to subcutaneous injections, we will recall the causes, consequences, and possible corrective actions of LHs, stigmatizing the fundamental role of therapeutic education and hoping that all this can interest all the actors who revolve around the management of insulin therapy, which is too often underestimated and hastily addressed by health professionals, who probably prefer to dedicate time to titration of therapy. Ultimately, our aim is to provide the reader with a practical review of injection errors resulting from incorrect insulin injection techniques, analyzing the leading causes of error and the consequences of these errors, while also providing advice and suggestions to overcome all this.

Keywords: diabetes; insulin injection; lipohypertrophy; diabetes complication; education

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1. Foreword

Injectable insulin suffered from limited availability in the last century due to its extraction from the animal pancreas, but today it is theoretically unlimitedly available,

thanks to the large-scale production of fast- and long-acting synthetic analogs capable of brilliantly mimicking its physiological action. However, some countries still have reduced access to insulin due to limited economic resources.

However, to carry out its action adequately, the hormone must be correctly administered so that its regular and uniform absorption from injection sites allows it to enter the bloodstream predictably enough.

Best insulin administration modalities.

As of 2017, over 30 million Americans—nearly 10% of the population—had diabetes [1]. More than 1.5 million new cases of diabetes were diagnosed in 2015 [1]. The prevalence of both type 1 and type 2 diabetes is rapidly increasing, and by 2050, diabetes is expected to affect over 20% of adults in the United States [2–5]. The enormous economic burden of diabetes, including direct (medical) and indirect costs, is consequently bound to display some twofold increase from the 327 billion USD estimated in 2017 [3,6].

In 2021, the International Diabetes Federation (IDF) calculated that approximately 536 million 20- to 79-year-old people (9.2% of the adults) have type 2 diabetes mellitus (T2DM), and a further 1.2 million children and adolescents have type 1 diabetes (T1DM). Moreover, the number of adults with diabetes is bound to increase to over 642 million by 2030 and 783 million by 2045. In 2021, diabetes-related deaths among 20- to 79-year-old people in the world have been 6.7 million, 32.6% of which occurred in those under 60 years of age [7].

Subcutaneous administration has been the choice ever since the dawn of the insulin era, despite problems related to former animal extracts [8].

Besides people living with T1DM having been typically on insulin since diagnosed, approximately half of those with T2DM self-inject insulin at least once a day and, as stated above, suffer some related problems. These consist primarily of local complications, including subcutaneous nodules defined as lipodystrophies (LDs) caused by injection errors and responsible for altered activity of injected insulin [9–12]. The two most common forms of LDs are: (i) fibrosis, consisting of the accumulation of stiff, dense scar tissue at the injection site resulting from a chronic process triggered by repeated minor tissue trauma with the consequent inflammatory response [13–17]; (ii) lipohypertrophy (LH), a local accumulation of fatty tissue at the injection site. The latter process is thought to depend on local stimulation of adipocytes (fat cells) by insulin, which acts as a major anabolic hormone regulating lipid metabolism [18]. Over time, this stimulation leads to both excessive growth (hypertrophy) and proliferation (hyperproliferation/hyperplasia) of individual adipocytes [17,19].

Injection errors cause poor metabolic control, wide glycemic variability, and sudden, unpredictable hypoglycemic events. Such phenomena represent a severe health problem in terms of increased national socioeconomic burden and impaired patient quality of life (QoL) [18,19].

Much literature deals with insulin-related LDs. Some authors report an LH rate as high as over 60% in people with diabetes (PwD) self-injecting insulin [19]. Should this percentage be applicable worldwide, we could expect some 145 million PwD to have LH and thus to be at risk for poor metabolic control and severe micro- and macro-vascular complications.

This short introduction aims to outline that a correct injecting technique is as relevant as the hormone itself to attain optimal glucose targets and focuses attention on poor injection habits as possible mechanisms underlying metabolic derangement conditions and related health consequences.

We prepared the present narrative review to provide the reader with an update on correct injection techniques, causes, consequences, and best prevention strategies for injection errors. We also added practical suggestions on LH detection, including grids and

schemes, to optimize information records concerning LH sites and features in compliance with international recommendations.

To address the issue immediately, we will analyze the most relevant aspects of insulin injections non-conventionally, i.e., dealing with different arguments in paragraphs to catch the reader's attention more easily.

Methods

The information contained in this narrative review comes from a search performed in MEDLINE (through PubMed), Embase, and CENTRAL (through The Cochrane Library) databases on 20 January 2025, using the keywords "injection", "skin lipohypertrophy", insulin injection", "insulin administration", "injection technique", "skin insulin complication", "hypoglycemia", "unexplained hypoglycemia", "glycemic variability", "insulin injection knowledge", " insulin injection practice", "insulin injection attitude", "insulin delivery", "injection devices AND insulin", "insulin injection recommandations". We selected clinical trials, recommendations, case series, clinical cases, and commentaries, as well as randomized, observational, and cross-sectional studies published in English from 2000 to 2025. We limited the publication date because diabetes care and insulin therapy standards have changed in the past decades, thus potentially influencing the results. Exclusion criteria were using automated pumps or other sensor-augmented devices for continuous subcutaneous infusion or animal insulin or studies oriented to general diabetes complications/comorbidities (i.e., other than skin complications) or other non-LH diabetes-related issues. We also performed a hand search of references for the included studies to retrieve other relevant publications not indexed in searched medical databases.

Three authors (F.S., G.G., and S.G.) performed data extraction independently. All discrepancies between authors (reviewers who reviewed the selected papers) were discussed and resolved. Extracted items included study design, baseline population characteristics, details of anti-hyperglycemic therapy, analyzed outcomes (HbA1c, glycemic variability, uncontrolled glycemia, hypo/hyperglycemia, daily insulin doses, insulin delivery systems, injection devices, injection-related skin complications, insulin injection technique recommendations, attitude and knowledge, costs related to insulin injection, and education), and their definitions.

Far from generating a meta-analysis, we prepared a narrative review following a logical path as follows:

1. Introduction
2. Noninvasive insulin delivery systems
3. Insulin pens, needles, and syringes
4. Insulin-induced skin lipohypertophy
5. Leakage phenomenon
6. Insulin injection knowledge, practices, and attitude
7. Role of therapeutic education
8. Conclusion
9. Appendix A: Correct LH manual skin search sequence
10. Appendix B: What should not be missing from a clinical recall
11. Appendix C: Checklist for best LH identification
12. Appendix D: List of countries where G33/4 mm and G34/3.5 mm needles are available

2. Introduction

Insulin is a double amino acid chain and, therefore, cannot follow the oral route. Instead, it must be injected because the digestive processes would degrade it. The subcutaneous tissue has consistently been chosen for injection because of its uniform yet relatively limited vascularization, in contrast to underlying muscles that are richly vascularized and would lead to tumultuous and irregular absorption. Indeed, accidental insulin injections into muscles carry a very high risk of hypoglycemia. In particular, if injected intravenously or intramuscularly, the basal insulin analog called glargine is absorbed like a rapid analog, thus triggering hypoglycemia due to the high doses chosen for its predicted constant throughout the subsequent 24 h [20].

The 2016 recommendations on injection techniques suggest the utilization of short 4 mm/32 G pen needles to grant correct insulin administration in both lean and fatty people, as the outer skin layer thickness is independent of BMI, gender, or race [21].

Since then, technology has produced thinner and shorter needles, i.e., 3.5 mm/34 G needles [3]—for which we provide in the Appendix the list of countries where they are available, still lacking clear evidence of superiority over the others, yet eventually beneficial for people living with diabetes (PWD) having specific features, including slender subjects with thin subcutaneous fat panniculus, sarcopenic patients, or small children. The 4 mm/32 G needles are suitable for the latter individuals [22], provided that the pinching maneuver is performed [9] (Figure 1).



Figure 1. Pinching maneuver, consisting of lifting skin and subcutaneous tissue fold between the fingers so as not to inject insulin into the underlying muscle (source: personal archive).

Sixty insulin-treated patients randomized into two groups volunteered to compare straight 32- and tapered 34-gauge 4-mm needles for usability and preference and to report eventually occurring insulin injection-related adverse events. Then, their investigators analyzed the relationship between patients' preferences and background characteristics, including thumb force measured by manual muscle testing [23]. All proved to have sufficient thumb force to push the injection button regardless of needle type. Moreover, despite perceiving significantly different feelings of insertion smoothness or pain during insulin delivery, they declared no difference in overall preference, pointing out both needles' overall satisfactory clinical usability and safety.

When using insulin syringes, people with diabetes (PwD) should consider that needles are 8–12.7 mm long on average and, therefore, carry a high risk of getting into the muscle unless implementing the pinching maneuver and injecting at a 45° angle to the skin [9] (Figures 1 and 2).

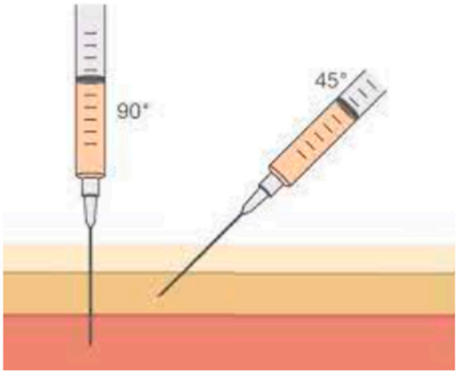


Figure 2. Schematic representation of insulin injection using a syringe equipped with a 12.7 mm long needle, with an angle of 45° to prevent the tip of the needle from ending up in the muscle tissue.

3. Non-Invasive Insulin Delivery Systems

Non-invasive insulin delivery systems could overcome the disappointingly poor PwD compliance with injectable insulin therapy. Within this frame, various research groups have proposed oral, buccal, pulmonary, nasal, intraperitoneal, and transdermal routes [24–27] without commercial success because of their difficult-to-manage method or relatively unpredictable dose delivery.

However, there are numerous limitations to using the airway as an alternative to the subcutaneous route. First, insulin cannot be administered by inhalation in young children because they cannot inhale correctly and in allergic subjects, including those with asthma or chronic broncho-pneumopathies or bronchodilator users (albuterol) [28]. Secondly, such a route is impractical for high doses. Finally, there is no absolute certainty that the programmed does correspond to those administered. Furthermore, irritation of the airways or local intolerances may occur in the long term [9].

Despite granting better patient compliance and adherence by avoiding drug pre-systemic first-pass metabolism, the proposed microneedle solution is also controversial because injections still cause pain, and the tissue is not sufficiently expandable to receive high eventually required insulin doses [27–29].

An exciting alternative to insulin injections, i.e., the needle-free jet transdermal administration proposed several years ago, still has a marginal role in insulin therapy despite distributing insulin evenly under the skin, which is different from traditional needle injections that concentrate the hormone within a small area. The reasons for this marginal role may be numerous: costs, acceptability, ease of use, safety, precision, efficacy, availability, etc. For example, the National Health System may not provide reimbursement for its use.

A recent self-controlled, cross-over study on intensive insulin treatment with needle-based injections versus needle-free injections in 65 hospitalized patients with T2DM showed better glucose levels and less pain with needle-free insulin injections. However, the authors did not provide any data on efficacy, safety, and dose precision in a less controlled home environment [30].

However, it is now undergoing improvement attempts through continuous technological innovations (Figure 3) [31,32].

Finally, we must consider that, despite not fully recovering from the disease, all insulin-treated PwD dream of the possibility of getting oral therapy. In principle, this is prevented by proteases, which inactivate protein molecules. However, phase 3 trials are underway with insulin micro-encapsulated in nano-carriers equipped with protease inhibitors preventing inactivation. Currently, the effectiveness and safety of such an approach remain to be proven [33–35].

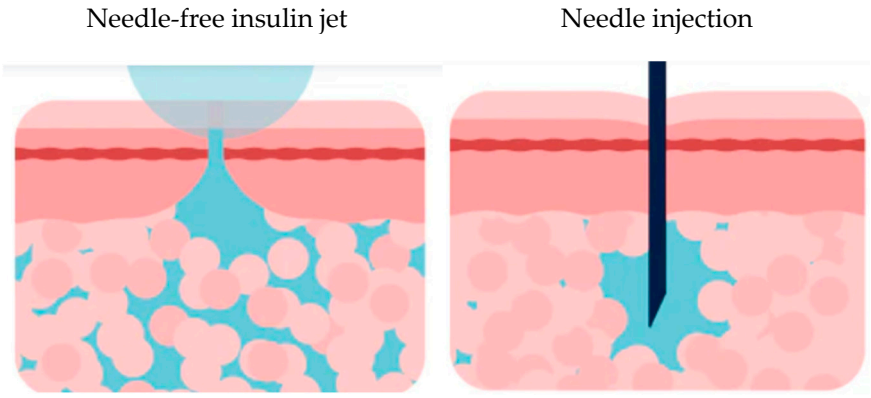


Figure 3. Schematic drawing of insulin delivery directly through the skin without a needle (**left**), and traditional needle injection (**right**). Note that in the first case, insulin is distributed uniformly in the subcutaneous tissue, while in the second it remains concentrated in a single point.

4. Insulin Pens, Needles, and Syringes and Technological Progress

In addition to traditional insulin syringes, still largely used worldwide, insulin pen use is increasing. Pens are certainly more comfortable to use and guarantee significantly greater dosing precision. However, they require specific educational training from health professionals at the start of insulin therapy for all the actions needed to reach the final act of administration. Compared to syringes, whose needle varies from 8 to 12.7 mm in length and most often a 29 G external caliber (Gauge, G), pens allow you to choose the length of the needle, down to 4 mm, and the gauge down to 34 G (see Appendix A–D) [22,36].

Moreover, the longer the needle, the higher the risk of intramuscular injection, as described in Table 1 [37].

Table 1. The monthly rate of intramuscular injections is related to the length of the needle used. (Source: Gibney MA. Curr Med Res Opin. 2010, 519-30, modified, reference [37]).

Needles Length (mm)	% Intramuscular Injections
12.7	45
8	15
6	6
5	2
4	0.4

However, despite being generally considered low-tech devices, pen needles have different features from one another as follows: (i) to guarantee stability and conservation, the external casing must be composed of waterproof synthetic material; (ii) to be easily seen by users and removed before the injection, the internal protective casing must be colored and non-transparent; (iii) to prevent the skin from being traumatized at the time of injection (as sometimes happens if the user exerts vigorous pressure), the implant base must be wide [36–39] (Figures 4–7).

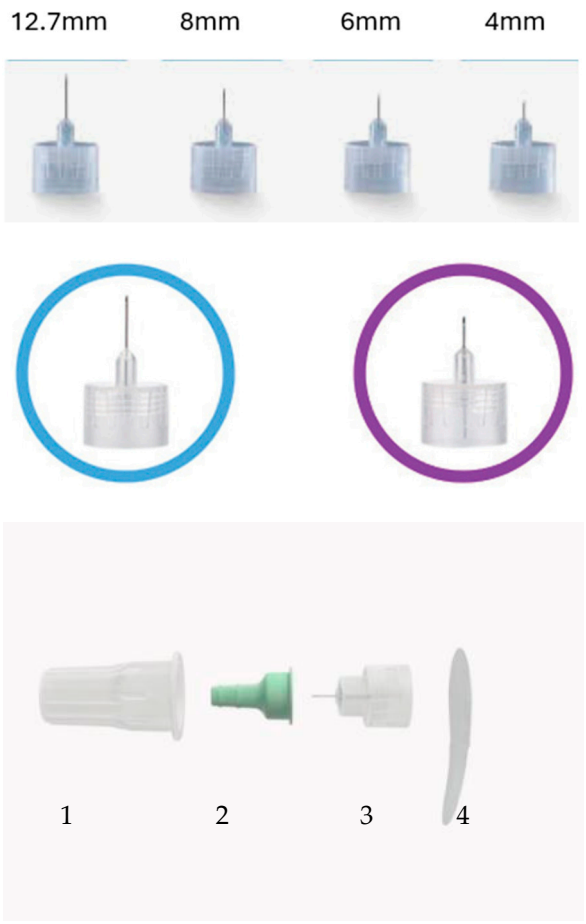


Figure 4. Insulin pen needles of different lengths (**top**). In the middle panel, detail on the comparison of an 8 mm (**left**) and 4 mm (**right**) needle. In the lower panel from left to right you can see (1) the external needle container, (2) the needle tip protection, (3) the needle, and (4) the hermetic and waterproof closure of the container.

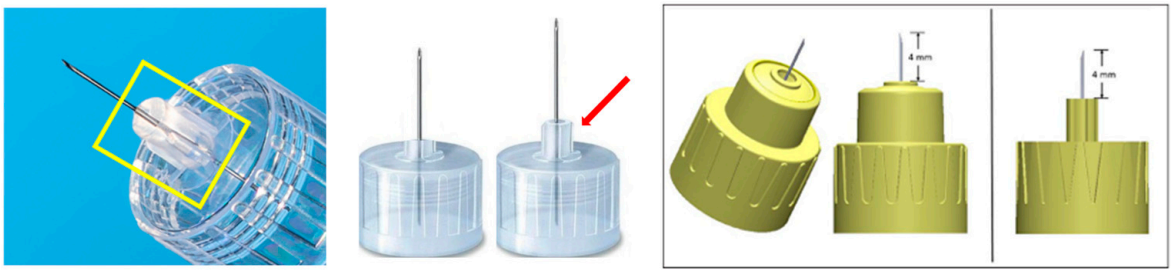


Figure 5. Needle base design can influence the way pressure is concentrated at the injection site. A non-posted, contoured base first concentrates at the injection site but then distributes forces across the skin surface (source: personal archive).

There is still no literature evidence of the 3.5 mm/33 G needles' superiority but only of non-inferiority compared to the 4 mm [22,36] ones. However, they can be helpful in very young children or thin people with a slim build and with little subcutaneous adipose tissue. The internal caliber of the needle and its lubrication are essential to let insulin flow inside it and get into the subcutaneous tissue more easily. The wider the internal lumen, the better the flow and the less force needed to push the insulin pen piston. Advanced thin-wall and extra thin-wall technology have made it possible to obtain a larger internal caliber for the same external caliber without weakening it while reducing the G. (Figure 8). However, if too small, an internal caliber inevitably requires people to exert a greater force on the pen's

plunger, thus potentially preventing people with hand joint or muscle-tendon problems from performing full-dose injections. Typical examples of such situations are represented by carpal tunnel, thickening of the palmar aponeurosis, trigger finger, tenosynovitis, arthritis and arthrosis, gout, finger amputations, or merely advanced-age sarcopenia.

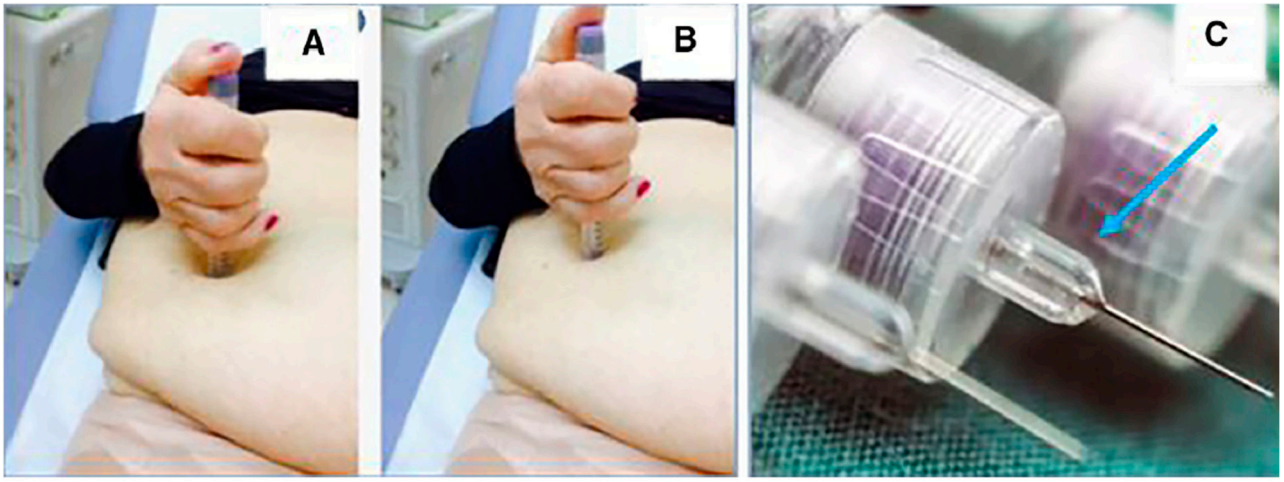


Figure 6. The **left** panel (**A**) shows stronger pen pressure into the skin (deep skin hollow) at the time of injection than in the **right** (**B**). The needle cone (**C**), if pressed too hard, can cause trauma to the skin and bruising (source: personal archive).



Figure 7. Bruising at the injection site (**a**,**b**). Lateral view of an LH nodule coming together with bruising (**c**), best seen after magnification (**d**) (source: personal archive).

No less important is the laser-assisted geometry of the needle tip with 3 or 5 cuts and without burrs along the incision line of each cut, which guarantees easier penetration and extraction from the tissues and, therefore, better injection comfort (Figure 9) [40–44].



Figure 8. Schematic representation of the wall thickness of the traditional (regular wall), thin (thin wall) and ultra-thin (extra-thin wall) needle, respectively of a progressively larger internal caliber (source: personal archive).

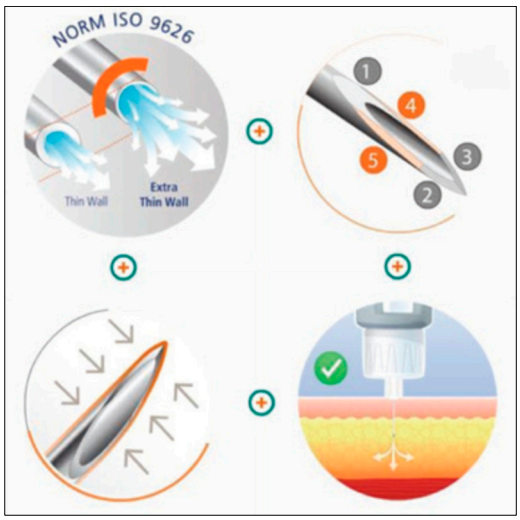


Figure 9. Schematic representation of multi-edged needle sharpening and increased insulin flow through ultra-thin-walled needles (**top left**) (source: personal archive).

Thus, injection remains the main administration route for insulin, and the needle dominates the scene because of its technological characteristics. The above-mentioned tip geometry and facet number influence skin penetration effort and pain experienced during administration, i.e., the main features granting safe injections with the least possible discomfort [17–22].

Additionally, the manufacturer must guarantee the compatibility of a needle with the thread of pens of different brands or with bayonet coupling through experimental tests proving injection safety and programmed insulin dose release, besides compliance with ISO 11608-2022 for standard certification. This document specifies requirements and test methods for single-use, double-ended, sterile needles intended for use with some needle-based injection systems (NISs) requiring a non-integrated double-ended needle according to ISO 11608-1M [45].

Figure 10 shows the different threading of two insulin pens to highlight the various ways of needle insertion [19,43,46–49].



Figure 10. Comparison with a pen equipped with thread and grooves for bayonet needle connection and a pen with thread only (source: personal archive).

Regarding how many times PwD should use a needle, Figure 11 shows the tip of the sealed needle compared to that of needles used one or more times. The trauma caused by reused needles varies depending on the state of the tip. Furthermore, for needles used several times, the problem of sterility and possible infections at the injection site arises, which are far from rare [19]. Indeed, the sealed outer protection provides the needle with sterility until exposure to open air among injections. Insulin may also crystallize within the fluid inside the needle; in that case, every further injection may result in trauma to the skin. In truth, the recommendations on correct injection techniques published in 2016 [21] resulted from a meeting attended in Rome by 150 experts from 50 nations around the world in 2015. One of the principles established there is that each needle should serve only one injection (one needle = one injection). Conversely, in recent years, some papers have been published that seem to support the idea of being allowed to reuse the needle at least five times before getting it deformed and potentially traumatic [50–52]. However, it should be considered that myriads of needles are produced by many different companies with very different structural and technological characteristics. They often lack certifications concerning adherence to the ISO or safety, quality, clinical trial, and user satisfaction directives. Therefore, for each of these, we should have evidence and, possibly, the opinion of people who use them for injections every day. Furthermore, economic factors could influence such observations, especially if they come from countries with non-universal healthcare systems or low per capita income. This element points to the need to use needles only once.

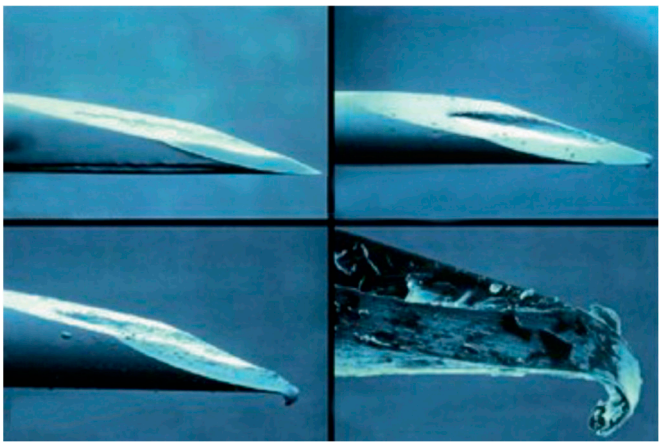


Figure 11. Microscopic image of 4 needles: the (**top left**) needle is new; the (**top right**) was used only once; the (**bottom left**) three times; the (**bottom right**) needle over five times. (source: personal archive).

5. Insulin-Induced Skin Lipohypertophy

The main local complication of insulin injection errors is represented by skin lipohypertrophies (LHs) at the injection sites [9,53–57].

LHs are extremely frequent PwD on insulin. Their prevalence spans from 2% to 68% [50,57] depending on the identification method, the experience of professionals involved, race, qualitatively and quantitatively adequate national device availability, educational intervention effectiveness, and compliance with national and international recommendations [58].

LHs are due to failure to rotate the injection sites, reuse of the same needle several times, use of ice-cold insulin, and insulin's anabolic properties [9,54].

Injection errors, and especially administration performed into LH nodules, cause erratic insulin absorption [57–61] with consequent poor glycemic control, acute complications including unpredictable hypoglycemia, and increased costs [58,60–63].

LHs are associated with poor metabolic control, frequent and unexplained hypoglycemia, high glucose variability, and increased rates of micro- and macro-vascular complications [52,53].

The sites where LH are present are only those where PDs inject insulin, mainly abdomen, thighs, arms, often symmetrically and even simultaneously in multiple sites. More rarely, LH are observed in buttox [62]. LH are made up of large adipocytes [17,58], but microadipocytes and areas of fibrosis are often present, with a low inflammatory cellular component, especially in the perivascular area or in areas of apoptosis where megadipocytes die [58].

In clinical practice, LH is usually diagnosed by physical examination, that is, visually and by palpation [55,56]. The most common presentation of LH is large, visible, and aesthetically displeasing mounds. However, increasing evidence suggests LH exists in various forms, many of which are not easily seen or palpation-detectable [54] (Figure 12).

As evident from the lack of uniformity in the approaches to visual and palpation examination methods between countries despite apparently common physical examination procedures, new methods have emerged to detect LHs, including skin ultrasonographic scanning (USS) [39–41]. Indeed, skin US is a more refined and precise method for diagnosing LHs than the clinical one [39–42], yet time and money constraints hinder its widespread utilization.

Based on ultrasound scanning, which represents the diagnostic gold standard, LHs can be classified as hypoechoic, hyperechoic, or mixed [15].

Structurally, LHs are composed primarily of large adipocytes [17,58] but often also contain micro-adipocytes, fibrous tissue, and a few inflammatory cells distributed especially around the small vessels and close to the mega-adipocyte apoptosis phenomena.

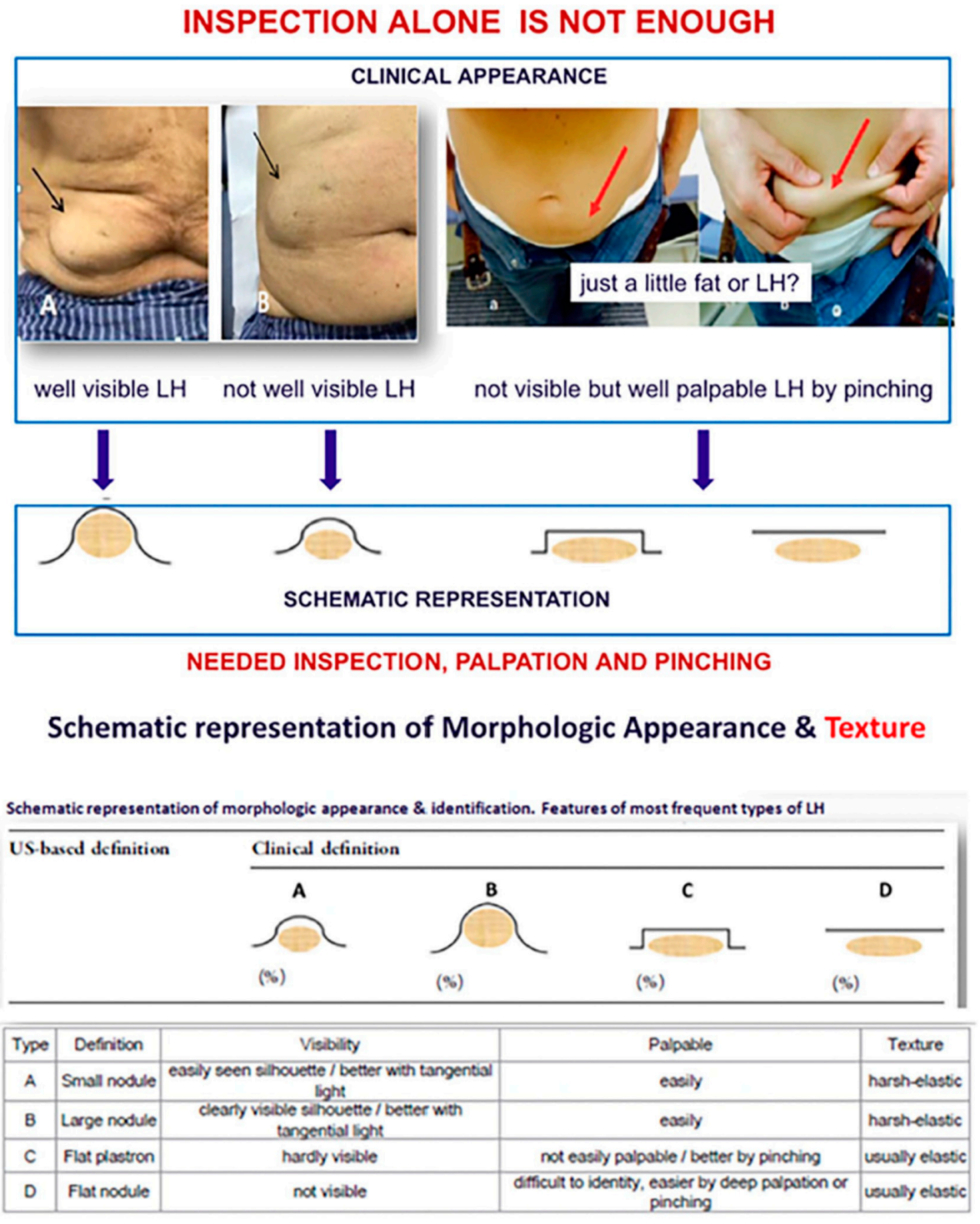
Combined palpation technique by expert and specifically trained HCPs grants good chances of success when based on (i) light and superficial firstly, then tough, deep, accurate palpation of injection sites, (ii) repeated site handling, (iii) careful site visual inspection using tangential and frontal light sources, (iv) pinching technique utilization (Figures 12 and 13) [56,57,62].

A recent meta-analysis, based on data from 26,865 patients, showed that LHs are a common health problem with a worldwide prevalence of 41.8% (95% CI: 35.9–47.6%) among PwD [42]. However, when considering studies that specifically utilized USS, these figures can rise as high as 86.5%, suggesting an underappreciated prevalence of this complication [54,63–67].

Published studies suggest that many insulin-treated patients have significant deficiencies in their injection technique. They often fail to ensure proper site rotation and prefer injecting insulin into LH nodules, as these areas are less pain-sensitive [66].

Available data indicate that injections into LH areas may occur in up to 55.3% of PwD on insulin [65–68].

A lack of thorough understanding of the possible LH consequences of LHs may make healthcare providers and individual patients unaware of the reason for the inefficacy of anti-hyperglycemic treatment. Driven by the high number of PwD and the high prevalence of LH, this represents an un-noticed global health problem.



Type	Definition	Visibility	Palpable	Texture
A	Small nodule	easily seen silhouette / better with tangential light	easily	harsh-elastic
B	Large nodule	clearly visible silhouette / better with tangential light	easily	harsh-elastic
C	Flat plastron	hardly visible	not easily palpable / better by pinching	usually elastic
D	Flat nodule	not visible	difficult to identity, easier by deep palpation or pinching	usually elastic

Figure 12. Images of the main types of insulin-induced skin LHs and schematic representation of their physical characteristics (source: personal archive).

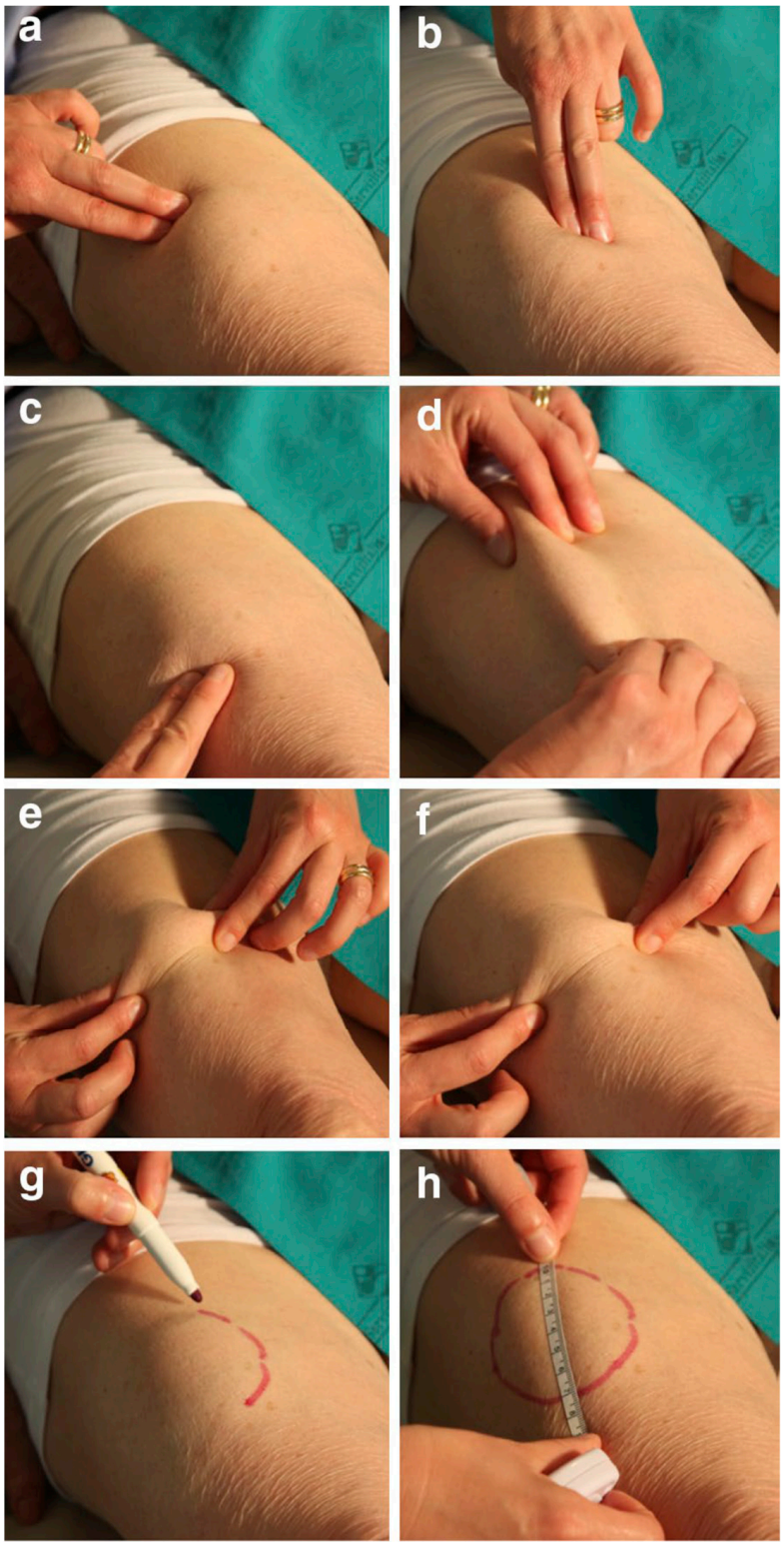


Figure 13. Lipohyertrophy identification technique. The figure shows how to identify an LH lesion after a thorough inspection of the area by performing repeated vertical and horizontal fingertip movements and around it (**a**–**c**), pinching it (**d**–**f**), and marking it (**g**) and how to finally measure it (**h**). (source: personal archive).

Aside from the apparent esthetic influence on patients' well-being and self-image, pharmacological studies suggest that different structural properties of LH lesions may affect insulin absorption and metabolism [68]. Insulin release from LH-affected tissue is considered slower and more unpredictable than normal fat tissue, which may result

in excessive insulin doses required to achieve a pharmacological effect [68]. However, despite device (syringes vs. pens), insulin preparation (pre-mixed vs. human insulins vs. analogs), or age (adults vs. children) related differences, the available clinical evidence of a direct relationship between the presence of LHs and poor glucose control with a high hypoglycemic risk is universally accepted.

Indeed, many studies reported an increased risk of poor glycemic control, high glucose variability, and episodes of unexplained hypoglycemia in patients with LHs [9,38,52,69–71]. For example, in a previous study, we observed that 46.2% of patients with LHs experienced one or more episodes of hypoglycemia compared with 6.8% of those without LHs [52].

In contrast, other studies found no such association [45,47–49]. The prevalence of hypoglycemia was comparable among patients with and without LHs [72].

However, we remind the reader that recurrent, unpredictable hypoglycemic events should themselves suggest LH presence [73]. Indeed, apart from a large amount of the already cited studies pointing to clinical LH-related risk, the meta-analysis of 26,865 PwD), by Wang et al. [63], reported a significantly higher rate of hypoglycemic events in patients with than without LH after logit transformation and pooled proportions according to the DerSimonian-Laird meta-analysis model [74]. Such discordant results come from relatively small case series and are apparently not free of possible methodological biases.

In Figure 14, the ultrasonographic appearance of two large periumbilical LHs is shown, in which two colliquated areas stand out containing a high concentration of insulin in a subject who complained of severe and frequent hypoglycemia, which disappeared after a long period in which the subject had no longer injected insulin into nodules [75,76].

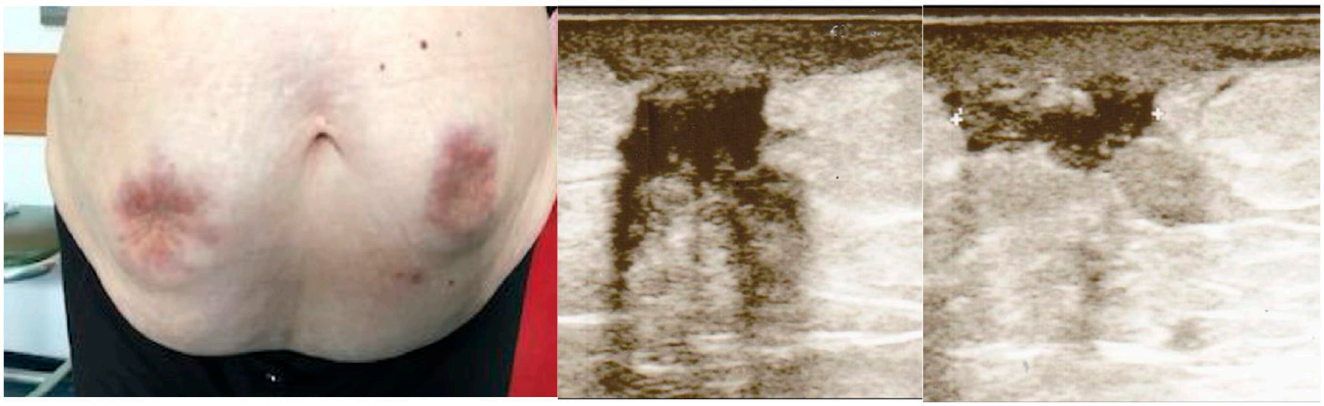


Figure 14. Two major LH swellings were evident at the two sides of the navel (9.8 cm large on the right and 8.6 cm large on the left), markedly protruding from the cutaneous plane (**left panel**). The central areas of both LH lesions were easily identified by sight and touch as umbilicated, hyperchromic, and cleft. Ultrasound scans of lipohypertrophic areas are also provided (**central and right panels**). The thickening of the dermis is clearly visible together with the central area of a colliquative nature. (source: personal archive).

In light of what is described so far, we can state that there is likely a progression over time of the LHs, which increase in volume until they reach large dimensions which undergo necrosis and colliquation phenomena as in the model proposed by Hashem et al., 2021 [76] (see Figure 15).

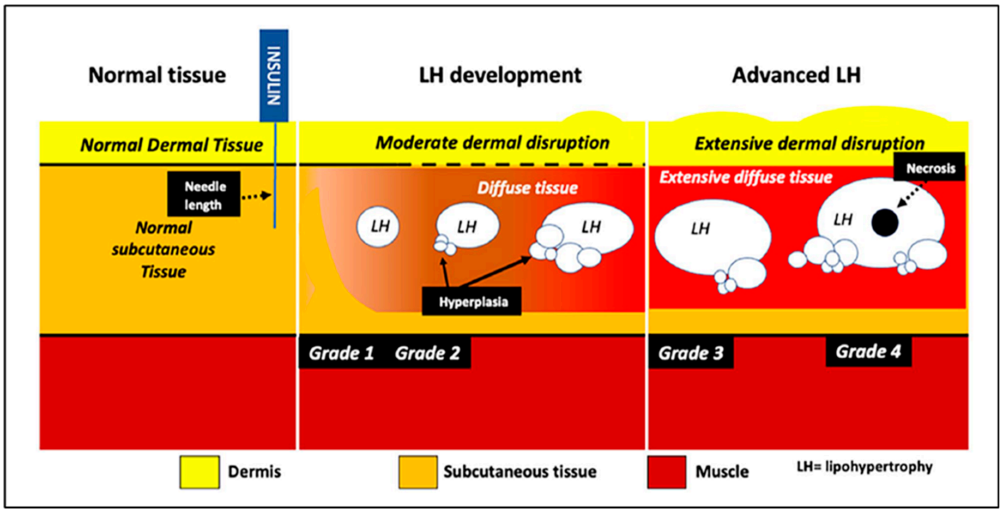


Figure 15. Conceptual model used to determine the severity of lipohypertrophy. Source: Figure reproduced from Hashem et al., 2021 [76] under the Creative Commons Attribution—Non-Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made are indicated, and the use is non-commercial. See http://creativecommons.org/licenses/by-nc/4.0/ (accessed on 30 October 2024).

6. Leakage Phenomenon

Another frequent skin complication is the so-called leakage phenomenon, characterized by liquid leakage immediately after removing the needle from the skin [49]. The liquid containing insulin must make its way into the subcutaneous tissue, and the smaller its volume and the greater the elasticity of the tissue itself, the more quickly it does so. As in the case of LHs, a sclerotic and inelastic subcutaneous tissue has poor distensibility, which hinders the diffusion of the liquid in the subcutaneous tissue and partly pushes it back through the needle penetration hole (see Figure 16). Although the phenomenon of the return of insulin after injection has been known for some time, to the best of our knowledge, studies dedicated to understanding its meaning have never been carried out. It is unknown why less leakage is more often seen in the abdomen than in the thighs. In our experience, making skinfolds is easier in the abdomen than in the thighs. This may indicate essential differences in tissue density, internal tissue pressure, or other mechanical factors of the subcutaneous layer and the skin. Even more so, in the presence of protruding or flat LHs under the skin's surface, there may be greater resistance to hosting a variable volume of insulin and a greater probability of leakage. However, dedicated studies are needed to gather evidence on the significance of this phenomenon.

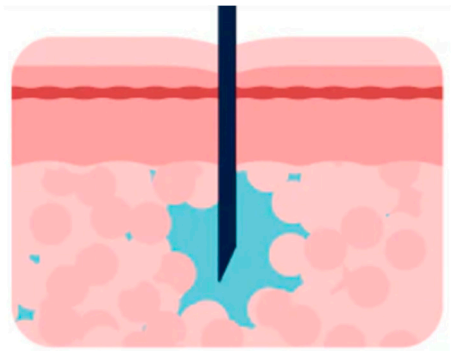


Figure 16. Schematic representation of the liquid that spreads through the needle into the subcutaneous tissue.

Common Injection Errors

One of the widespread injection technique errors is the way of holding the insulin pen. Holding the pen in the palm of your hand with fingers tightening it and using the thumb to press the plunger is the safest way to perform a complete injection by making full use of the muscular hand strength, mainly to keep the plunger pressed for several seconds at the end of the procedure. Conversely, holding the pen with the fingertips requires greater strength and risks performing an incomplete injection, especially if the subject has osteoarticular problems present in many elderly subjects (see Figure 17).



Figure 17. At the **top**, the pen held correctly allows the thumb to have adequate pressure, while at the **bottom**, the pen is held in such a way that it is difficult for the finger pressing on the plunger to exert the right force to give a complete injection and wait a few seconds while maintaining the pressure at the end of the injection (source: personal archive).

Finally, when noticing that the liquid does not flow through the needle during the injection, a pen user should check that the needle is screwed onto the pen with a skimpy movement, keeping the needle and pen on the same axis because an angled position of the two parts increases the risk of bending or breaking the internal part of the needle expected to pierce the upper rubber of the pen reservoir, thus preventing regular insulin flow into the subcutaneous layer (as illustrated in the clinical case published in this issue, (see Figure 18)).

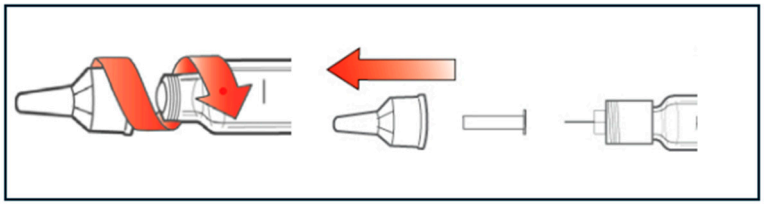


Figure 18. The needle must be screwed onto the pen, keeping both aligned on the same line so as not to bend the part of the needle facing the pen and prevent the passage of insulin.

7. Insulin Injection Knowledge, Practices, and Attitude

The presence of so many insulin injection-related LHs in PwD causes problems for individuals in terms of QoL and National Health Systems regarding social and economic burden. Various groups besides ours have tried to explain such a high LH prevalence by setting up specific studies on knowledge and practice among patients, nurses, and physicians.

In 2017, Robb et al. [77] used a questionnaire to investigate insulin knowledge and practice in a cohort of 164 district nurses in Northern Ireland. They found district nurses scored 53.1% on average. Total knowledge scores were slightly higher (58%) than total practice scores (46%). Nevertheless, 79.4% of district nurses felt confident enough, and 6.3% felt highly confident in managing diabetes. The authors identified deficits in district nurses' knowledge and practice concerning insulin action, dosage, storage, injection site technique and rotation, hypoglycaemic/hyperglycaemic management, pharmacological action, and prescription format.

In a nationwide multi-center cross-sectional survey, patients, nurses, and physicians were randomly chosen using the stratified cluster sampling method from 250 primary, 150 secondary, and 100 tertiary care hospitals. In total, 10,694, 2643, and 2816 eligible questionnaires were collected from patients, physicians, and nurses, respectively [78]. Overall, 78.2% of T2DM patients failed to attain the target hemoglobin HbA1c. Hypoglycemic episodes and lipohypertrophy occurred in 19.8% and 34.7% of the patients, respectively. Needle reuse (odds ratio, 1.19; 95% CI, 1.07 to 1.33) and incorrect injection site rotation (odds ratio, 1.32; 95% CI, 1.16 to 1.51) were associated with failure to attain the target hemoglobin A1c. Additionally, 48.9% of physicians and 20.4% of nurses had an inadequate knowledge domain score. Therefore, poor glycemic control, occurrences of injection-associated complications in PwD, and poor knowledge domain scores of a subset of physicians and nurses highlight the importance of regular assessment and education regarding diabetes drug injection techniques for physicians and nurses.

A Chinese cross-sectional nationwide study evaluated insulin injection knowledge, attitudes, and practices of 223,368 nurses working and injecting insulin at grassroots hospitals, including community health service centers and township clinics and secondary and tertiary care hospitals [79]. Their average knowledge questionnaire score was 13.70 $\pm$ 3.30 and 35.19% had a poor knowledge score. The mean attitude score was 17.18 $\pm$ 2.69 for the study nurses; merely 3.15% had a poor attitude score. The mean practice score of the study population was 83.03 $\pm$ 8.16 and only 0.88% had a poor practice score. Pearson correlation analysis showed a significant correlation between the knowledge score and the attitude score (r = 0.29; $p < 0.001$), the knowledge score and the practice score (r = 0.27; $p < 0.001$), and between the attitude score and the practice score (r = 0.56; $p < 0.001$). A multi-variate analysis revealed that nurses with higher knowledge scores were also more likely to have higher attitude scores and practice scores, and nurses with higher attitude scores were also more likely to have higher practice scores. In conclusion, Chinese nurses have a good attitude and behavior towards insulin injection, while their knowledge of insulin injection is insufficient. Additionally, knowledge of insulin injection can directly or indirectly affect insulin injection behavior through attitude, indicating that hospitals should formulate unified insulin injection norms and regularly organize relevant training and assessment to improve nurses' knowledge, attitude, and behavior of insulin injection.

A cross-sectional study surveyed the knowledge and practice preferences of 289 nurses who worked in units performing subcutaneous injections in a university hospital in Turkey [80]. More than half of the nurses did not use a rotation chart; they swabbed the skin before a subcutaneous injection, and they always pinched the skin at the injection site; 50% of nurses reported consistently administering subcutaneous injections at an angle of either 90 or 45 degrees. Most nurses injected in less than 30 s and waited for 10 s before withdrawing the needle. They did not apply massage to the site following the injection. Nurses' knowledge of subcutaneous injections was at a moderate level, highlighting that their best practice in subcutaneous injection administration and site selection could be improved.

Another Chinese study from the Guangdong province studied 19,853 nurses from 82 hospitals in 15 cities [81]. Among all nurses involved in this study, 22.3% had good knowledge, 75.9% had a good attitude, and 92.7% had good behavior. Pearson's correlation analysis showed that knowledge, attitude, and behavior scores were significantly correlated, and nurses need timely updating. The influencing factors of knowledge, attitude, and behavior included gender, age, education, nurse level, work experience, type of ward, diabetes nursing certification, position held, and most recent insulin administration.

These data highlight the need to improve the knowledge of PwD, besides the knowledge, attitudes, and behaviors of healthcare personnel on correct injection techniques and the consequences of errors made in their execution.

8. Role of Therapeutic Education

Since the 1980s, several literature reports have suggested that injection technique is as crucial for metabolic control as insulin type and dose [82–86]. The injection technique encompasses a range of procedures intended to facilitate the most consistent and least painful insulin delivery into the subcutaneous tissue. It includes considerations, such as injection site and needle length selection, angle of needle insertion, and skin fold lifting. The injection technique applied can significantly influence insulin pharmacokinetics (PK) and pharmacodynamics (PD). Hence, the correct technique helps avoid skin complications such as LH, local inflammation, and bruising, as well as the abovementioned metabolic consequences ending up in high HbA1c levels [9,19,30,38,52,54,57,63,67–70]. According to international and national recommendations, injection site rotation across large surfaces and avoidance of repeated needle reuse or 45° angling of 4 mm long needles into pinched skin are essential to avoid the abovementioned changes and ensure optimal insulin absorption [21,59,61].

Moreover, therapeutic efforts to keep glycated hemoglobin (HbA1c) within target levels quite often lead to an increased risk for hypoglycemic episodes (HYPOs) in insulin-treated patients [61]. HYPOs, especially severe ones, have significant clinical, social, and economic impacts [61]. From a clinical standpoint, they can cause a broad set of symptoms ranging from general discomfort to seizures and coma, or even sudden cardiac arrhythmic death or lethal brain damage in the case of long-term glucose deprivation [73,87–98].

Therefore, it is crucial to inject insulin correctly. Notoriously, besides increasing direct and indirect health costs [18,50], repeated HYPOs severely affect patient health by increasing cardiovascular and dementia risk [89,94]. Indeed, mild symptomatic HYPOs increase cardiovascular risk and elevate the risk of all-cause hospitalization/mortality, resulting in an excessive economic burden [18]. Glycemic Variability (GV) due to improper injection technique is also a major cardiovascular risk factor in type 2 diabetes mellitus (T2DM) patients [95].

Nevertheless, given the high rate of LH lesions reported in the literature [19,57,67], it is reasonable to hypothesize that most clinicians visit PwD in too short a time frame to allow appropriate education on correct injection techniques, despite this being as crucial to effective diabetes management as discussions about glucose control and dose adjustments [9,96]. Conversely, health-related quality of life and treatment satisfaction are correlated and affected by a complex interplay between clinical and socioeconomic variables. Some negative impacts on the quality of life of subjects living with DM are associated with the insulin treatment strategy applied and perceived poor metabolic control. Anecdotal reports indicate that proper IT education reduces GV and HYPOs in LH subjects [96].

Evidence of the effectiveness of therapeutic education in reducing HbA1c levels, glucose variability, and frequency and severity of HYPOs was provided by our 24-week multi-center case-control clinical trial on 318 people with T2DM randomized to structured,

intensive education on correct injection techniques with periodic educational reinforcements (Intervention Group, IG) or to a simple, initial educational intervention (control Group, CG) [18]. During follow-up, the intra-LH injection rate for the CG progressively decreased to 59.9% ($p < 0.001$), a much smaller decrease than seen for the IG (1.9%, $p < 0.001$). Only the IG presented significant decreases in HbA1c (8.2 ± 1.2% vs. 6.2 ± 0.9%; $p < 0.01$), GV (247 ± 61 mg/dl vs. 142 ± 31 mg/dl; $p < 0.01$), insulin requirement (−20.7%, $p < 0.001$), and prevalence of SeH (severe HYPOs) and SyH (Symptomatic HYPOs) (which dropped dramatically from 16.4 to 0.6% and from 83.7 to 7.6%, respectively; $p < 0.001$). In the IG group, costs—including those due to the reduced insulin requirement—decreased significantly, especially those relating to SeHs or only SyHs, which dropped to 25.8 EUR and 602.5 EUR, respectively ($p < 0.001$).

The durability of the educational action was also the subject of study because we had no information on this topic. As the treatment continued, in a second investigation called ISTERP-2, the intensive treatment group of the previous study was divided into two subgroups of 79 subjects each [97]. The first subgroup continued to receive educational refreshers regularly (IG), while the second no longer had the educational support (CG) experienced in the previous six months. The IG subjects maintained and even improved the good behavioral results attained during the ISTERP-1 study by further reducing both the rate of injection technique errors ($p < 0.001$) and the size of LHs ($p < 0.02$). Conversely, those in the control group progressively abandoned best practices, except for the use of ice-cold insulin, and, consequently, had significantly higher HbA1c levels and daily insulin dose requirements at the end of the follow-up than at baseline ($p < 0.05$). In addition, as expected from all the above, the rate of HYPOs also decreased in the IG ($p < 0.05$), resulting in a significant difference between groups after six months ($p < 0.02$). Data provide evidence that intensive, structured education refresher courses have no outstanding durability, so repeated refresher courses occurring at least 6-month intervals are needed to positively affect people with T2DM, contributing to prevention and long-term rehabilitation.

A further study called ISTERP-3 has provided us with information on the economic effects of therapeutic education on correct injection techniques [98]. The objective of the study was to perform a 52-week follow-up of 713 insulin-treated patients with T2DM and LH to detect any differences in the occurrence of HYPOs and related healthcare costs as well as in LH rates and injection habits between an intensive education intervention group (IG) and control group (CG) provided with a single educational session at the starting point. All participants were trained in accurately self-monitoring blood glucose and recording all HYPOs for 6 months, which allowed baseline recordings before they were randomized into the IG, comprising 395 insulin-treated subjects undergoing repeated, structured multimodal education on correct injection techniques as a longstanding behavioral rehabilitation strategy, and the CG, comprising 318 subjects receiving the same structured, multi-modal educational session only initially. Changes in LH rate and size and improvements in patients' performance were prominent in the IG and only slight and transient in the CG. A striking difference in the rate of decrease in HYPOs was also apparent between groups. Indeed, estimated costs of health interventions for SeH and SyH HYPOs, which, in both groups, at baseline were on the order of 70,000 EUR and 9300 EUR, respectively, at the end of follow-up decreased by 5.9 times and 13.7 times, respectively, in the IG, and by only approximately half in the CG. The paper provides full details of the changes occurring as a result of intensive education.

From these three trials, we can draw information to validate the usefulness of structured therapeutic education and realize that the effect of initial education alone is insignificant. Such results provide evidence of the virtual worthlessness of a single training session on injection techniques, which is typical of worldwide daily clinical practice, and easily

explains the extremely high prevalence of LHs in insulin-treated patients. Conversely, highly positive effects on LH prevalence and size and costs expected from decreased HYPO rate were obtained in the IG, thus proving that repeated, structured, multi-modal education is needed for sustainedly successful results. To the best of our knowledge, ours is the first 18-month randomized trial in the field. If our experimental model were to be used as an effective, longstanding behavioral rehabilitation strategy and adapted to real-world settings universally, LH prevalence and costs related to their clinical consequences would drop drastically.

However, we can only achieve this ambitious goal with the firm, relentless commitment of universities, scientific societies, and patient associations. It would provide considerable institutional savings and improve the quality of life for people with diabetes.

9. Conclusions

The present excursus on insulin administration modalities, injection technique errors, and related consequences leads to the following conclusions:

1. The most usual administration method relies on automatic systems, including pens. Despite the widespread utilization of syringes in several countries, pens are comfortable, practical, and safe, provided patients comply with a few simple rules as from the detailed 2016 Recommendations [21] currently under updating [98];
2. Pen utilization grants the choice of short needles, a crucial issue considering that shorter and thinner needles are safer (by avoiding inadvertent intramuscular injections) and preferred against PwD's discomfort;
3. Progress in technology has allowed dedicated factories to produce needles complying with the ISO 2022 norms and endowed with a much smaller outer diameter than before, appropriate tip geometry, and easier skin penetration;
4. Injection technique errors like missing site (abdomen, lateral arm/thigh sides, and buttocks), needle reuse, ice-cold insulin administration, and long with a pointed attachment to the barrel can cause local complications including LHs, bruising, and infections besides precipitating the so-called Leakage Phenomenon, i.e., injected fluid loss after needle extraction;
5. LHs are fatty nodules consisting of mega-adipocytes interspersed among fibrous streaks due to repeated trauma and insulin anabolic properties [9,17,58] without immune-allergic reactions [58];
6. It is easy to identify protruding LHs, although accurate diagnostics rely only on ultrasound scans;
7. LHs come with significant glucose variability, unpredictable hypoglycemic events, and poor metabolic control that, in turn, associated with faster diabetes complication progression;
8. The high LH rate observed in PwD on insulin points relentlessly to the poor level of education granted by healthcare providers (HCPs) to the patients since the very beginning;
9. According to the results of various worldwide surveys, PWD knowledge and abilities concerning insulin injection techniques and LH prevention are poor, and HCPs need updates and sensitization on the relevance of the issue;
10. Literature data unequivocally shows that structured education grants PwD lower LH rates and size over time. However, in the absence of regularly occurring refresher meetings, positive education effects typically fade away within a few months.

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Informed Consent Statement: All patients gave written consent for releasing their data and/or images in this article. All the images in this manuscript are schematic drawings or photos taken from the personal archive and are produced with the consent of the people portrayed (anonymously). Figure 15 is reproduced from Hashem et al. 2021, [76] under the Creative Commons Attribution—Non-Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made are indicated, and the use is non-commercial. See http://creativecommons.org/licenses/by-nc/4.0/ (accessed on 30 October 2024).

Data Availability Statement: No new data were created or analyzed in this study.

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Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviation

AMD = Scientific Association of Diabetes Specialists; OSDI = Italian Diabetes Nurses Scientific Association; PK = pharmacokinetics; PD = pharmacodynamics; HYPOs = hypoglycemia; IG = Intervention Group; CG = Control Group; SeH = severe HYPO; SyH = Symptomatic HYPO.

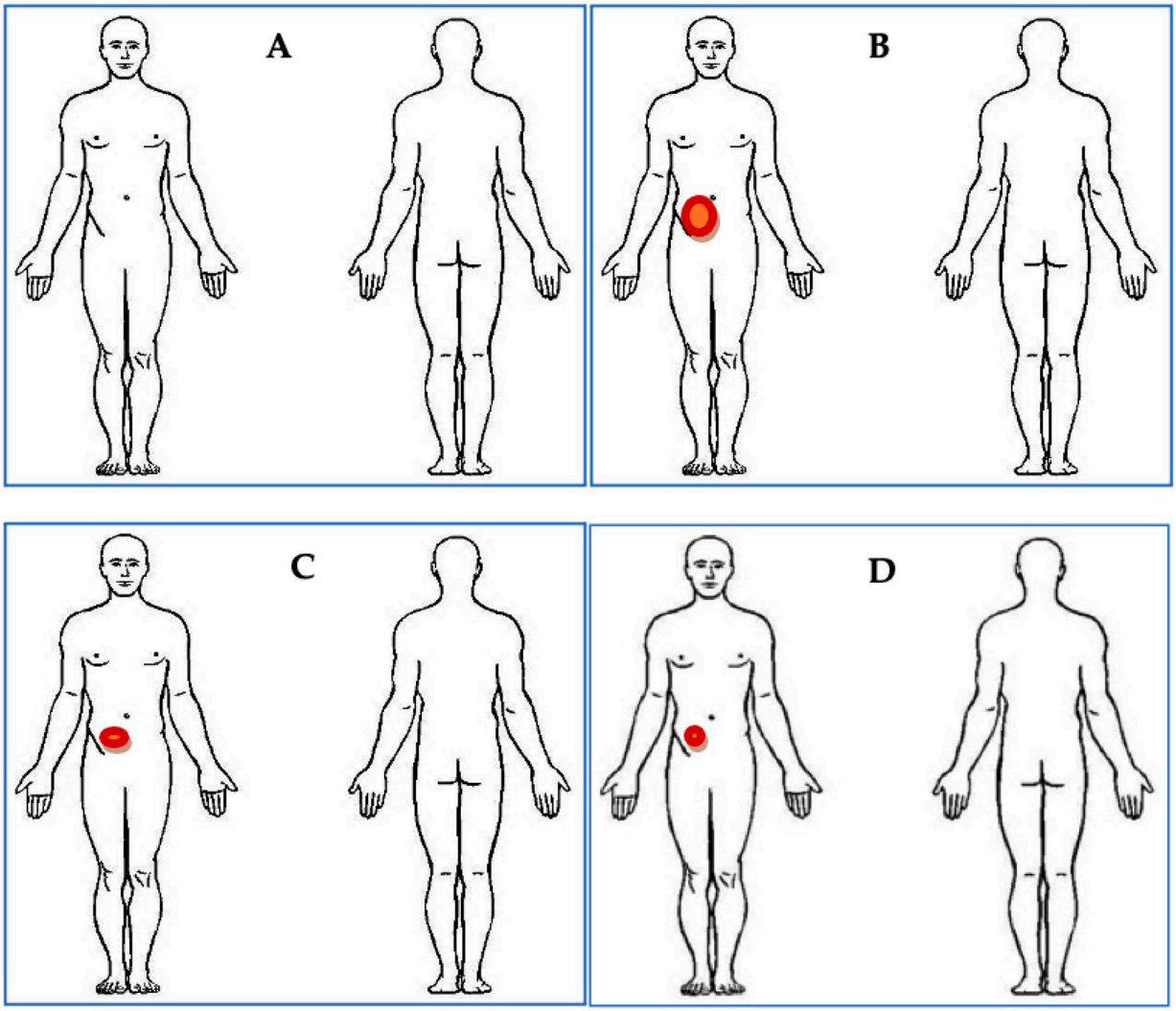
Appendix A

	Correct LH Manual Skin Search Sequence
1	Have the subject 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
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 him/her 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 identifying clear palpable LHs
11	Show identified LHs to the patient, explain why they form, what metabolic consequences they entail, and why the need to perform the insulin injection correctly
12	Give precise and motivated indications on how to inject insulin correctly (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 of insulin injection errors

Appendix B

What should not be missing from a clinic recall

Clinical Records should allow the recording of the location, dimensions and physical characteristics of skin LHs, so as to be able to follow their evolution over time (see figure and grid below)



LH Features	Right Arm	Left Arm	Right Thigh	Left Thigh	Right Hemi-Abdomen	Left Hemi-Abdomen	Right Buttock	Left Buttick
Present								
≥4 cm								
<4 cm								
Protruding								
Fat								
Hard-Elastic								
Soft								

Figure A1. 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 (source: personal archive).

Appendix C

In addition, diabetes-related clinical records should include a detailed checklist devoted to all actions needed to identify LHs in insulin-treated patients, as follows:

Checklist for better LH identification

- 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 perform injections correctly?
- 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 with 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 the 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 removing the pen from 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?
- 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?

Appendix D

List of countries where G33/4 mm and G34/3.5 mm needles are available (*data provided by the manufacturer*) (Fonts, bold and colours identify different regions, countries and needle types).

G34 × 3.5 mm		**G33 × 4 mm**	
	EUROPE	**WESTERN ASIA**	**EUROPE**
HONK KONG S.A.R	*ITALY*	*SAUDI ARABIA*	*ITALY*
TAIWAN	*GREECE*	*IRAQ*	*SLOVENIA*
AUSTRALIA & NEW ZELAND	*SPAIN*	*QATAR*	*GREECE*
AUSTRALIA	*MALTA*	*U.A.E.*	*PORTUGAL*
NORTHERN AMERICA	*SAN MARINO*	*JORDAN*	*MALTA*
CANADA	*GFRANCE*	*IRAN*	*SPAIN*
U.S.A.	*SWITZERLAND*	*TURKEY*	*FRANCE*
	UKRAINE	**ASIA**	*NETHERLANDS*
	POLAND	*TAIWAN*	*SWITZERLAND*
	LITHUANIA	*MONGOLIA*	*BELGIUM*
	PORTUGAL	*HONK KONG S.S.R.*	*UK*
	NORTHERN AFRICA	*VIETNAM*	*DENMARK*
	ALGERIA	*MALAYSIA*	*SWEDEN*
	EGYOT	*BRUNEI*	*FINLAND*
	LIBYA	**AUSTRALIA & NEW ZELAND**	*UKRAIN*
	TUNISIA	*AUSTRALIA*	*BELARUS*
	WESTERN ASIA	**NORTHERN AMERICA**	*POLAND*
	SAUDI ARABIA	*CANADA*	*ROMANIA*
	U.A.E.	*U.S.A.*	*CROATIA*
	KUWAIT	*SOUTHERN AMERICA*	*BULGARIA*
	ARMENIA	*BRASIL*	**NORTHERN AFRICA**
	JORDAN		*LYBIA*
	IRAN		*TUNISIA*
	ASIA		*WESTERN AFRICA*
	MALAYSIA		*NIGERIA*
	JAPAN		*GHANA*
	MONGOLIA		

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