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RESEARCH ARTICLE

A Journey Through Guidelines, Consensus, Curriculum of Educators and Clinical Practice on Insulin-Induced Skin Lipohypertrophy: From the Earth to the Moon

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Summary
This minireview wants to draw the readers' attention to a neglected complication of insulin therapy, i.e., lipohypertrophy due to injection errors. The considerable diffusion of lipohypertrophy represents evidence of a lack of education and monitoring. This phenomenon occurs despite international recommendations on correct injection techniques in the latest American Diabetes Association Standards of Medical Care in Diabetes edition. There are no precise indications in the literature for well-organized courses for educators like those promoted by the International Diabetes Federation. The damage caused by LH, such as poor glycemic control, significant blood sugar variability, and unexpected hypoglycemic events, represents a high risk for acute and chronic complications of diabetes and an increase in health and social costs. Unfortunately, as reported by the WHO, health costs tend to increase spontaneously over time and have been increasing recently with the COVID-19 pandemic, which has also enormously contributed to new cases of diabetes. For all this, a call to action is required for errors in insulin injection techniques across the board, involving university programs, specialization programs, joint efforts of all scientific endocrinology-related societies, manufacturers of insulin and injection devices, and Ministries of health.
Key words: diabetes, insulin, injection technique, lipohypertrophy, education

Currently, two thousand ninety-six publications from the last 20 years are listed on PubMed under the heading “skin lipodystrophy” (LD). They drop to 1one thousand five hundred and eighty-two after papers on congenital, familial, or HIV-related skin LDs are ignored.

However, the first cases of the LD form called "lipoatrophy" (LA) were first described in 1922 [1], i.e.., immediately after insulin entered the market. Over the years, LA was the most frequent LD. It depended on impurities of insulin preparations coming from the animal or not yet compliant with the best 1980sì rules of purification technology, responsible for immune-allergic processes wearing out the subcutaneous adipose tissue at the injection sites [2,3]. However, currently, LAs represent less than 5% of all insulin-induced skin LDs. Recent studies do not report inflammatory cascade cells in skin biopsies but only non-specific morphological adipocyte abnormalities suggesting insulin resistance [4].

Currently, 95% of insulin-induced cutaneous LDs are represented by lipohypertrophy (LH), an accumulation of subcutaneous fat related to the anabolic effect of insulin and injection technique errors consisting of repeated microtraumas from repeated needle reuse on restricted skin areas as a consequence of missed injection site rotation or ice-cold insulin utilization [5-7]. Identifying smaller LH lesions, especially those still in formation, is not always easy because they are not visible but only palpable by expert hands according to a structured method [8-10]. Indeed, LH appears as a soft, smooth, raised area several centimeters in breadth and can contribute to erratic insulin absorption, increased glycemic variability, and unexplained hypoglycemic episodes, which explains the considerable variability of LH frequency reported by different papers [11,12]. More recently, skin ultrasound scanning was proposed to detect non-visible and poorly palpable LHs at insulin injection sites. Indeed, despite proving sensitive, specific, and very effective, especially in terms of patient education [13], this method remains confined to scientific studies and fails to enter the clinical routine due to the high cost of ultrasound devices and the time required for a thorough and complete examination of all injection sites.

According to the ARNO-CINECA Observatory records, about 24% of the approximately 4 million persons with diabetes surveyed in Italy in 2019 (ISTAT 2021) [14], corresponding to almost 1 million patients [15], are treated with insulin of various types. So, based on the rough 40% average (i.e., 37% to 48%) frequency of ultrasonographically diagnosed LH lesions [16,1], we can expect 400,000 persons with diabetes to have LH lesions from wrong injection techniques!

It is not conceivable for anyone seeing an insulin pen for the first time to learn how to autonomously screw a needle onto it and inject the drug properly. Evidently, a doctor or nurse explained how to do it, at least at the start of treatment. So, how can such a high frequency of LH from a bad injection technique be explained? Recent studies by our group have documented that even a multimodal and well-structured training conducted on insulin-treated patients has a durability of no more than six months, after which patients tend to forget the teachings received and the skills achieved [18]. Only after a further educational path lasting another six months do patients return to follow the instructions received [19,20]. Beyond this, however, we have no studies capable of establishing the persistence of patient acquisitions. Indeed, based on a recent survey of ours aimed at knowing who, when, and how taught patients to inject insulin, about half of people cannot remember or believe they have learned it from friends or relatives already self-injecting insulin [21].

This scenario is disheartening, mainly because LH has not only esthetic but also metabolic consequences proved by a solid mass of literature, including glycemic variability (GV), unpredictable and often very severe hypoglycemic episodes (HYPOS), poor metabolic control [18-20], associated health and social costs [21], and a poor quality of life.

Yet, there is no lack of information in the literature on how to properly inject insulin and the consequences of a poorly made injection. First of all, the International Diabetes Federation (IDF) precisely defines the skills required to be an educator in diabetology and, concerning insulin injections, offers structured courses to acquire them through a "Curriculum of diabetes educators". The latter, given in English or Spanish, consists of 11 Modules of 12-hour duration (suggested three hours per week for four weeks), a low cost (i.e., 50 € for low-income countries (LIC) and 75 € for the others [22], with specific objectives to be achieved as listed in Table 1.

Table 1. Learning Objectives of Diabetes Educators on insulin handling

At the end of this module the learner will be able to:	
1	Discuss the various devices available for insulin administration
2	Describe the administration of insulin using different methods, including syringes, pens and pumps
3	List the factors affecting insulin absorption
4	Discuss the importance of care on insulin handling and administration
5	Identify the right way of storing insulin

In chapter 9 of the Standards of Medical Care 2020 [23], the American Diabetes Association put forward precise indications to let patients and caregivers understand the importance of correct insulin injection techniques for optimal glucose control and treatment safety. Recommendations have also been published elsewhere, outlining best practices for insulin injection [24].

In greater detail, proper techniques include injecting into appropriate body areas (including the abdomen, thigh, buttock, and upper arm), routinely site rotation, special care of injection sites to avoid infection or other complications, and avoidance of inadvertent intramuscular (IM) – instead of subcutaneous - insulin delivery. Apropos of the latter, as IM insulin absorption differs according to the activity of the muscle, thus becoming unpredictable, such an error can easily be responsible for the frequent and unexplained hypoglycemia described in several reports. The risk of insulin reaching the muscle instead of the subcutis is increased in younger, leaner patients using long needles and preferring limbs to the abdomen or buttocks. Recent evidence, including a study performed on adults with obesity, suggests shorter (i.e., 4-mm) pen needles be more effective and well-tolerated [25]. Injection site rotation is also necessary to avoid LH. So, patients and caregivers should receive education about that and learn how to identify and avoid areas of LH. The above-mentioned critical components of a comprehensive diabetes medical evaluation and treatment plan [26] hold the potential for improved clinical outcomes and, therefore, are crucial to ensure an effective treatment.

Despite all the above, the recommendations and guidelines remain disregarded mainly, and skin LH remains a neglected complication of insulin injection. Let's try to bring diabetes and insulin treatment back to a planetary dimension to better understand the phenomenon we are analyzing.

In 2021, the International Diabetes Federation (IDF) calculated that 536.6 million people between the ages of 20 and 79 (9.2% of adults) in the world have diabetes and that an additional 1.2 million children and adolescents (0-19 years) have type 1 diabetes. The number of adults with diabetes is also expected to increase to over 642 million in 2030 and 783 million in 2045 (Figure 1) [27]. In 2021, deaths attributable to diabetes in the world between the ages of 20 and 79 were 6.7 million, 32.6% of the total in individuals under the age of 60 [28].

Figure 1. Estimates of the global prevalence of diabetes in the 20–79-year age group (millions) from 2000 to 2021. (from IDF ATLAS 2021, modified) [27].

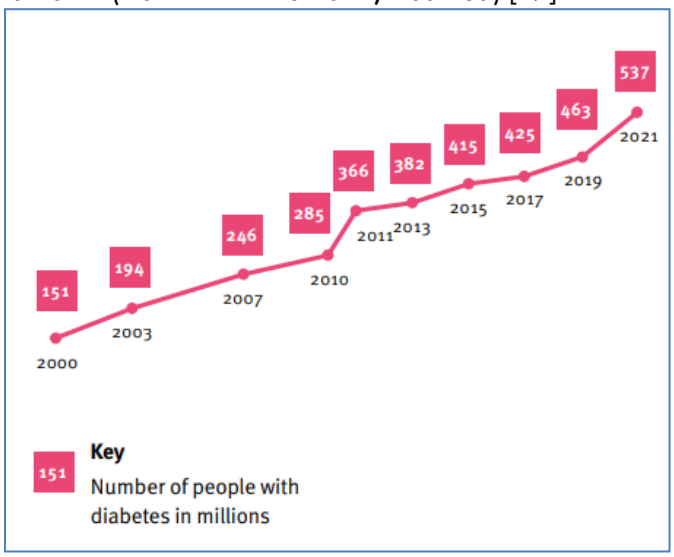
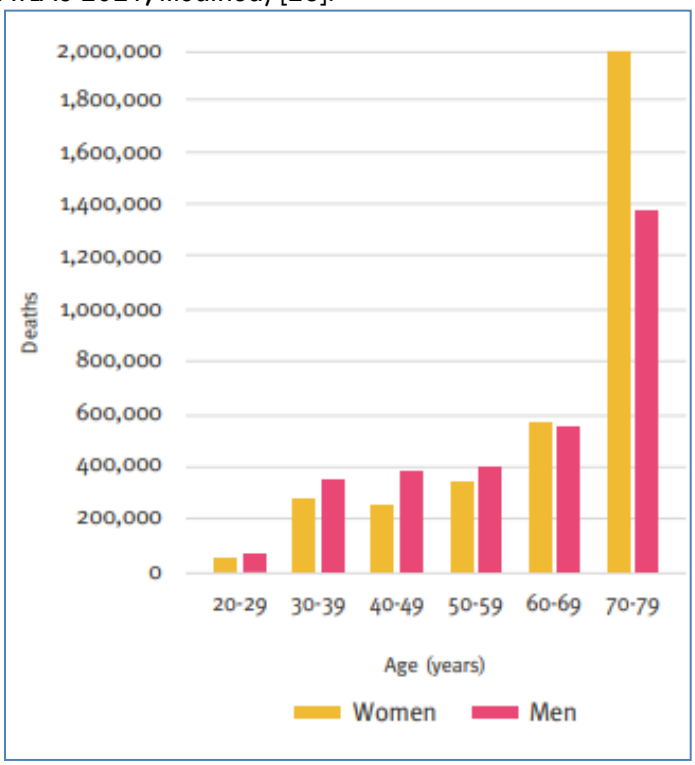


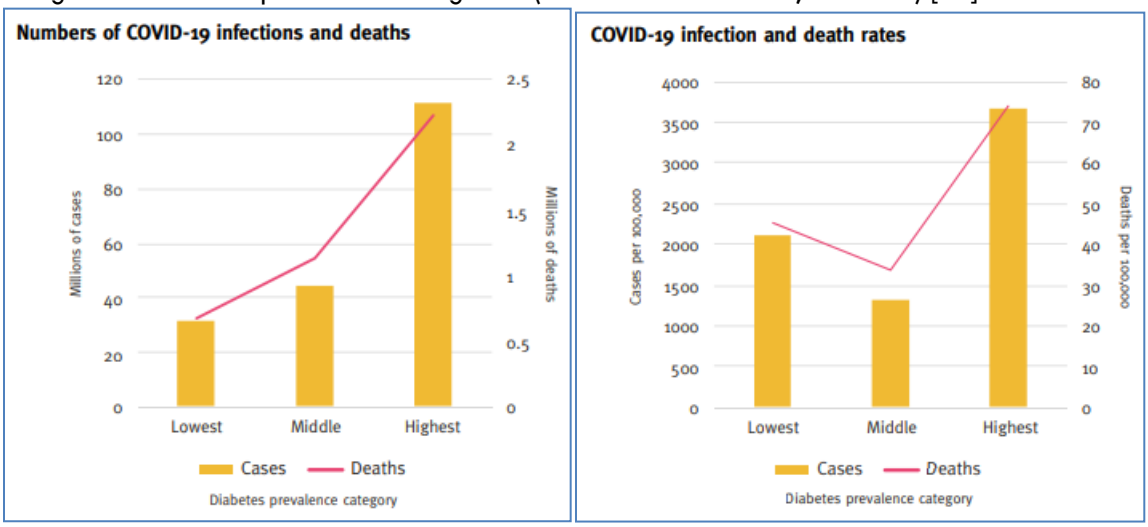
Figure 2. Number of deaths due to diabetes in adults (20–79 years), by age and sex in 2021 (from IDF ATLAS 2021, modified) [28].



Thus, the increase in cases of diabetes and subjects on insulin is constantly growing. Still, another phenomenon is bound to increase those numbers, especially those of insulin-treated people: the SARS-CoV-2 pandemic (COVID-19).

Indeed, the COVID-19 pandemic has caused a severe strain on Healthcare systems, economies, and our way of life. Since its December 2019 outbreak in China, COVID-19 has spread rapidly, triggering the World Health Organization (WHO) declaration of a global pandemic in March 2020 [29]. Since the beginning, people with diabetes proved to be at high risk for severe complications, including COVID-19 pneumonia, acute respiratory distress syndrome (ARDS), and respiratory failure [30-32]. They needed hospitalization, mechanical ventilation, and other life-sustaining measures much more than peers without diabetes (Figure 3) [32–34]. After that, papers in the field got progressively more numerous, thus letting scientists explore the association between diabetes and the risk of hospitalization and death from COVID-19. So, from the analysis of 282 studies, patients with diabetes hospitalized with COVID-19 appear to have a 2.3 times higher risk of death than those without diabetes. Also, age seems to be an essential risk factor for COVID-19 severity and mortality in hospitalized people with diabetes. Many older adults live in long-term care facilities, where early disease outbreaks proved particularly severe and deathful [35-42]. After adjusting for age, sex, and other risk factors, poor glucose control - as reflected by high HbA1c levels - was associated with worse COVID-19 endpoints, including hospitalization, ICU admission, and death [43-46]. However, fewer studies investigating the relationship between blood glucose levels at the time of access and adverse outcomes were inconclusive [43-53]. Indeed, long-term diabetes complications, i.e., cardiovascular and kidney diseases, which are also mortality risk factors in hospitalized people, may explain at least some excess risk of adverse diabetes consequences observed in the case of COVID-19 [51,54].

Figure 3. Cumulative number of COVID-19 infections, and rate of COVID-19 deaths across countries according to IDF diabetes prevalence categories. (from IDF ATLAS 2021, modified) [28].



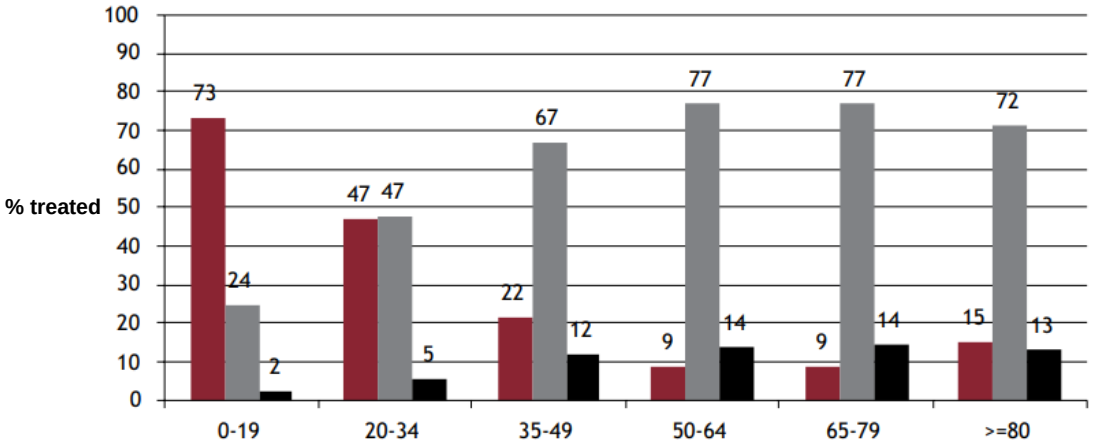
New-Onset Diabetes in Covid-19

So, diabetes is associated with an increased risk of severe Covid-19 [55]. Patients with Covid-19, in turn, often present new-onset diabetes and severe metabolic complications of preexisting diabetes, including ketoacidosis and hyperosmolarity, requiring exceptionally high insulin doses [56-58]. Such findings might depend on SARS-CoV-2 causing pleiotropic alterations of glucose metabolism, further aggravating the pathophysiology of preexisting diabetes or leading to new disease mechanisms. Besides the well-recognized stress response associated with severe illness, all of the above support the hypothesis of a potential diabetogenic effect of Covid-19.

From a clinical point of view, we feel like emphasizing that hospitalized patients with the severe disease need frequent blood glucose monitoring. Oral agents - especially metformin and sodium-glucose cotransporter-2 inhibitors - need to be stopped in those cases, and insulin is the preferred agent for the control of hyperglycemia [59].

Considering Italy, about 875,000 - out of the roughly three and a half million people of any age with T1DM or T2DM - are on either exclusive or combined insulin treatment (Figure 4) [60]. According to international estimates reporting a 37% to 48% LH rate [16,17], 323,000 to 420,000 subjects are expected to have LH. This data globally results in an imposing mass of people with diabetes and LH, demonstrating how little is done at an educational level.

Figure 4. Frequency and type of hypoglycemic treatment by age group. *Red columns: insulin; gray columns: oral hypoglycemic agents (OHAs); black columns: OHAs + Insulin.*



Conclusive remarks

From this analysis, albeit brief, we can conclude that: (i) the phenomenon of lipodystrophies due to incorrect insulin injection techniques is still widespread, despite the availability of curricular educational programs for diabetology educators, guidelines, and detailed consensus documents on how to inject and handle insulin correctly; (ii) the population with diabetes is constantly increasing according to the growth trend already reported by the WHO for several years and to the ever-increasing evidence of a diabetogenic role for the never-ending pandemic waves of COVID-19; (iii) insulin therapy takes on particular importance to improve the prognosis of people with COVID-19 either newly diagnosed diabetes in or already known as having diabetes.

In this view, compliance with correct injection rules represents a powerful therapeutic tool against the risk of nullifying the effect of poorly performed insulin treatment, which would severely endanger the health and well-being of patients with diabetes.

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Authorship

All named authors (Sandro Gentile, Ersilia Satta, Giuseppina Guarino, Teresa Della Corte, Giampiero Marino, Carmine Romano, Adalgisa Maffettone, Erika Eliana Heinke, Elvira Donnarumma, Romina Castellano, Salvatore Izzo, Iolanda Manzo, and Felice Strollo) meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article taking responsibility for the integrity of the work as a whole, and gave their approval for this version to be published.

Authorship Contributions

Sandro Gentile and Felice Strollo designed the study and wrote the article. Ersilia Satta, Giuseppina Guarino, Teresa Della Corte, Giampiero Marino, Carmine Romano, Adalgisa Maffettone, Erika Eliana Heinke, Elvira Donnarumma, Romina Castellano, Salvatore Izzo, Iolanda Manzo critically read and approved the paper. All authors contributed to data acquisition, critically assessed the results, and approved the final text. All collaborators critically read and approved the final text.

Disclosures

Sandro Gentile, Ersilia Satta, Giuseppina Guarino, Teresa Della Corte, Giampiero Marino, Carmine Romano, Adalgisa Maffettone, Erika Eliana Heinke, Elvira Donnarumma, Romina Castellano, Salvatore Izzo, Iolanda Manzo, and Felice Strollo have no financial interests to declare in relation to the present study.

Compliance with Ethics Guidelines

This study does not take into consideration data from directly observed diabetic patients, but is limited to analyzing data deriving from the skiing literature.

The list of members of the AMD-OSDI Study Group and Nefrocenter Research & Nyx Start-Up Study Group is available on Gentile S, et al. Adv Ther. 2022 May;39(5):2192-2207. doi: 10.1007/s12325-022-02105-5. Epub 2022 Mar 19

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