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Review

Why are so huge differences reported in the occurrence rate of skin lipohypertrophy? Does it depend on method defects or on lack of interest?

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ABSTRACT

Lipohypertophy (LH) is the most common skin complication of incorrect injection technique which does not only represent an aesthetic defect but also severely disrupts insulin pharmacokinetics/pharmacodynamics. As a consequence of that, hormone release is delayed and unexplained/unpredictable hypoglycemia occurs, both deteriorating metabolic control while negatively affecting adherence to treatment and quality of life. The economic burden due to unwanted intra-LH injections is accounted for by inappropriately high insulin requirements, increased emergency-related hospitalizations, and loss of work days. Greater attention has to be paid by diabetes care teams to education programs with periodic refreshers to achieve better metabolic control and reduce the economic burden of diabetes.

1. Introduction

In spite of detailed, recently delivered guidelines and recommendations concerning the topic [1,2], according to the most recent evidence the development/maintenance of skin lipohypertrophy (LH) at injection sites is strongly related to incorrect injection techniques (needle reuse, ice-cold insulin utilization, improper needle length/gauge choice, missed site rotation or utilization of the same spot within each site, etc) [3].

2. Clinical impact of LH

The metabolic consequences of LH are well defined, including poor glucose control, large glycemic variability and unpredictable hypoglycemia [4], all of which are known to represent major cardiovascular risk factors and to lead to chronic micro-vascular complications as well [5].

Many authors have recently reported on LH rate and metabolic consequences without providing details concerning the method they used to identify lesions: Table 1 summarizes data from three individual publications and some more studies contributing to the meta-analysis performed by Deng et al., in 2017 [6–9] (see Table 1). According to those 29 quite similar studies summing up to about 13,000 people with type 1 and Type 2 DM, LH prevalence ranged from 1.9% to 77.0%. Possible reasons behind such astonishing variability might be different insulin dosages and treatment durations, as well as, almost constantly missing information on needle length/gauge and on LH identification method. Referring to the latter, health professionals involved were extremely variable and their specific competence was also ill-defined (very often the terms "trained" or "experienced" were used, without any further details; moreover the diagnostic method was not elucidated).

3. How to recognize LH lesions

Some authors used self-administered patient questionnaires, others used ultrasonography, some more only stated that observation- or palpation-based diagnosis had been made by different people, i.e. a physician, a trained physician, a trained diabetes nurse, two investigators, a dermatologist, two experienced dermatologists, experienced pediatric diabetes nurses, diabetes

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Table 1
Overview of the prevalence of lipohypertophy in patients with diabetes mellitus. Data provided by reference n. 9 and integrated by three more papers (references n. 6, 7, 8).

Study ID	Year	Country	DM Type	Prevalence of LH (%)	Method for detection of LH	MNOS
McNally	1988	UK	NS	27.1	OAP by physicians	3
Hauner	1996	Germany	1 + 2	23.7	OAP by a trained physicians	3
Seyoum [6]	1996	Ethiopia	1 + 2	28.7	OAP by physicians	2
Ibarra	1998	Spain	1 + 2	52.0	OAP by a trained diabetes nurse	2
Partanen	2000	Finland	1	29.0	OAP by a diabetes specialist nurse	3
Raile	2001	German	1	43.8	OAP by two investigators	1
Strauss	2002	Seven European countries	1 + 2	27.0	OAP by a trained diabetes nurse	4
Teft [7]	2002	Scotland	1 + 2	57.0	OAP by a trained diabetes nurse	1
Pavlovic	2007	Serbia	1	1.9	OAP by two experienced dermatologists	3
Vardar	2007	Turkey	1 + 2	48.8	Observation and palpation techniques	4
Schober	2009	Austria	1	46.2	OAP by researchers	3
Coninck	2010	Sixteen Countries	NS	47.9	Self-reported by patients	4
Hajheydari	2011	Iran	1 + 2	14.5	OAP by one specialist physician	3
Cunningham	2013	Ireland	1 + 2	51.0	Observation and palpation techniques	3
Blanco	2013	Spain	1 + 2	64.4	Ultrasound examined, OAPby diabetes nurse	4
Ji	2014	China	2	35.3	OAP by trained diabetes nurses	4
Grassi	2014	Italy	NS	48.7	OAP by trained nurses	4
Munster	2014	Netherlands	1	34.8	OAP by experienced pediatric diabetes nurse practitioners	4
Binder	2015	Austria	1	20.0	OAP by medical staff	3
Berard	2015	Canada	1 + 2	24.6	Self-report by patients	4
Al Ajilouni	2015	Jordan	2	37.3	OAP by inspection and palpation	3
Li	2016	China	2	73.4	OAP by trained diabetes nurses and nursing postgraduates	4
Hayek	2016	Saudi Arabia	1	52.3	OAP by a trained diabetes educator	2
Youssef	2016	Egypt	1	23.7	OAP by dermatology team	2
Patil	2016	India	1 + 2	11.1	OAP by investigators/patient's questionnaire	3
Strollo [8]	2017	Italy	2	77.0	OAP by two trained physicians with a structured methodology	5
Ji	2017	China	1 + 2	53.1	OAP by trained study staff	5
Hemar	2017	Norway	1	47.4	OAP by trained specialist nurses	3

pediatricians, nursing postgraduates, trained diabetes educators and trained investigators (see Table 2).

For example, based on self-administered questionnaires, Patil et al. [10] found that "twenty five (11.1%) subjects had noticed persistent swelling at their injection sites suggestive of the LH", which does not seem to be the result of a clinical evaluation made by healthcare professionals. Conversely, a 77.0% LH prevalence was documented in a series of 387 people with T2DM [8] according to a structured LH investigation method utilized by well trained health professionals successfully involved in previous LH-related studies [11–13].

In addition to that, as pointed out by some authors, the variable LH prevalence among studies may be related to the lack of routine skin examination in diabetes clinics [4,14]. However, it may also be due to doctors/nurses having attained different levels of experience and even failing to stick to a clearly defined, validated identification methodology [9,15]. In fact, such lesions have extremely variable morphological features in terms of size, texture, and protrusion above the skin, as schematically shown in Fig. 1.

4. Recent methodology

Recently we published three papers dealing with best practice in LH identification [11–13] thereby underlining the importance of both operator's experience and lesion morphological features, including shape and size. In fact, LH lesions are usually protruding and have a medium-large diameter (up to several centimeters) but may also take the appearance of flat, hardly visible subcutaneous tissue thickening spots which can be detected only by trained professionals used to regularly pinch any skin areas suspected to be LH-affected (Fig. 1).

In particular, 60 patients were appropriately diagnosed by ultrasound as having LH. After that, 4 well trained clinicians and as many ill-trained ones were asked to identify lesions by blind palpation. A significant difference in the diagnostic ability was found between the two groups, being influenced by both training level and LH morphological features [12]. Therefore, widely spread low LH identification ability asks for appropriate education and refresher courses to be regularly organized in order to get wrong injection techniques corrected and thus reduce their often underestimated, yet invariably deleterious metabolic and economic consequences [16–18].

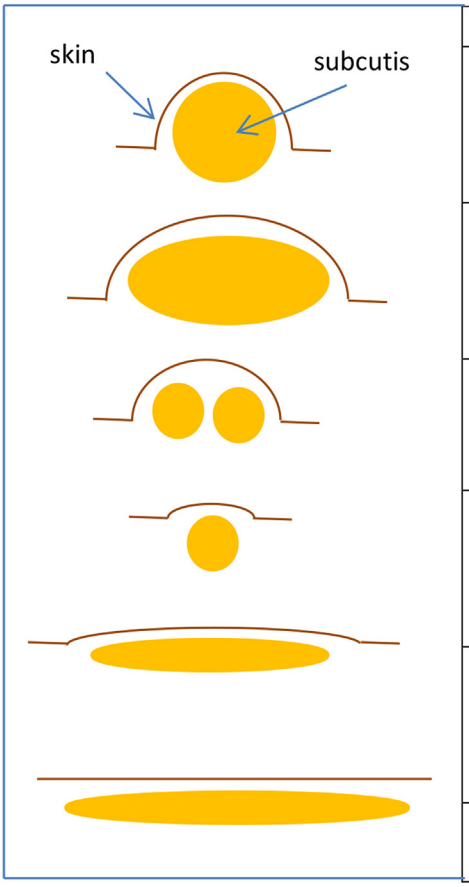
5. New insights and proposal

We would now like to point out another possibility to enhance LH diagnosis which has been devoted no attention in the literature, i.e. asking the patient to change from the orthostatic to the supine position or vice-versa during LH identification procedures. Figs. 2 and 3 clearly show how soft protruding LH lesions are less visible under clinostatic conditions. They refer to a type 1 DM patient who had experienced a dramatic body weight drop (17 kg in less than six

Table 2
Insulin-treated diabetic subjects (1219 [65%] with LH out of 1875).

BW (kg) CHANGES	n. (%)	BMI (kg/m^2)	SEX M/F	Age (years)	Diabetes Type 1/2	HbA1c (%)	GV$^{\&}$ (mg/dl)	Hypos$^{\$}$ (n/w)	LH $^{£}$ better l-to-S
NO	1154 (95)	30,5 ± 3.8	0,97	65 ± 7	192/962	9.7 ± 1.5	298	5 ± 2	4%
YES	65 [5]	24.2 ± 2.6	0.91	66 + 3	10/60	10.1 ± 0.9	301	6 ± 3	97%
p	<0,001	0.001	ns	ns	ns	ns	ns	ns	0.0001

GV$^{\&}$ = Glicaemic variability as previously defined (20); **Hypos$^{\$}$**: hypoglycemic episodes/week as mean of 24 weeks: **LH $^{£}$ better L-to-S**: changing position lying-to-standing improves the diagnostic the diagnosis of LH.



Type	Size, shape	Visible	Palpable	Texture
A	Medium, protruding	easily	easily	harsh / elastic
B	Large, protruding	easily	easily	harsh / elastic
C	Multiple small, protruding	easily	easily	harsh / elastic
D	Small, almost flat	hardly, better on tangential light	hardly, better by pinching	harsh / elastic
E	Large, almost flat	hardly, better on tangential light	only by pinching	usually elastic
F	Large, flat plastron	not at all	only by pinching	usually elastic

Fig. 1. Schematic representation of morphological characteristics and identification features of most frequent types of LH lesions.

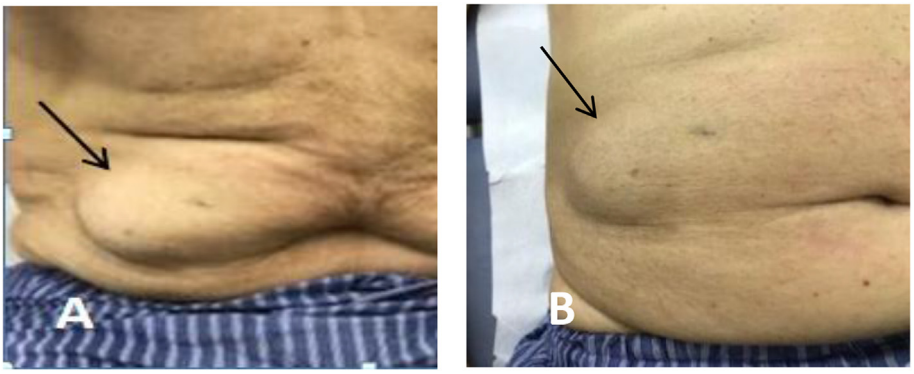


Fig. 2. Changes in standing (A) to lying(B) identification affecting features of large abdominal lipo-hypertrophic lesions. Panel A: on the right a large 12 × 8 cm lesion and on the left a smaller one (10 × 7 cm) are easily seen. In B panel a less evident right lesion is seen in the recumbent patient.

months), caused by severe metabolic derangement (HbA1c 11.6%) coincident with a foot plant ulcer requiring him to undergo amputation up to the ankle. The huge decrease in whole body weight obviously involved a marked reduction in both muscle and fat mass but, on a pathophysiological basis, cannot expect to have contributed to any structural changes in LH lesions, which became in fact more easily identified already at sight. This case triggered us to go deeper into this issue, so that,out of our 1875 insulin treated patient database, we selected those having LH ($n = 1219$, accounting for as high as 65%). Among the latter 1154 had kept weight-stable (WS) during the last few months while 65 had showed a 10%–20% weight decrease (WD) due to various reasons (including severe metabolic derangement, cancer, dementia, severe kidney failure requiring dialysis, etc.). 63 patients from the WD group (97%) *vs* 161 from the WS group (14%) were more correctly identified as having LH in the orthostatic than in the clinostatic position ($p < 0.001$ based on chi-square analysis).

Another practical hint for the health professional may be to take a strategic position with respect to the patient in order to have the lesion to reflect light at its best. If we carefully examine the sequence of images presented in Fig. 4, we can see that, being the patient standing upright, the para-umbilical skin swelling is more evident at a specific angle of tangential light (In this specific case, the diagnosis of hernia was ruled out by ultrasonography).

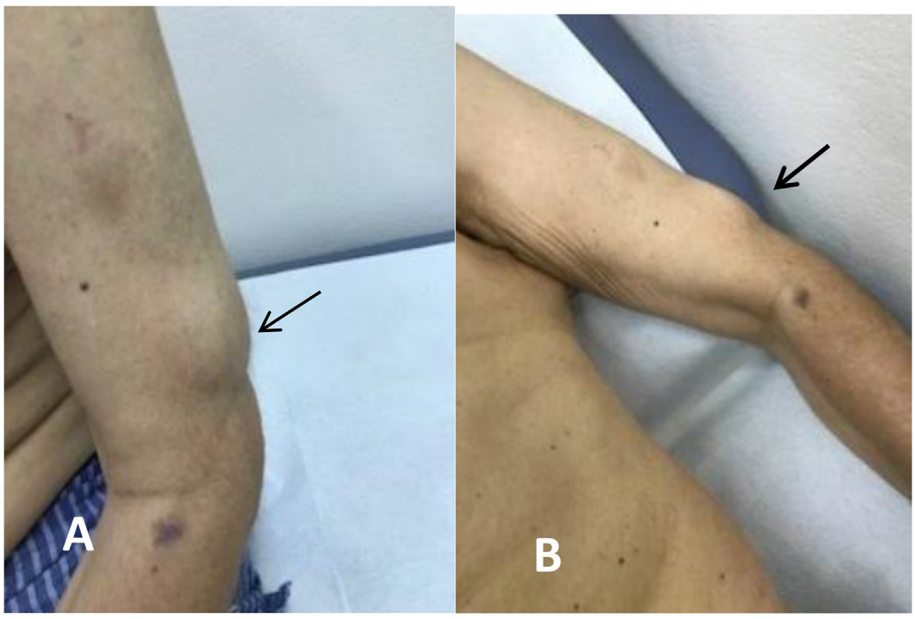


Fig. 3. Changes in standing (A) to lying(B) identification affecting features of the lesion present at the lower third of the left arm (due to repeated injection into the same site which is even wrong *per se*). Also in this case the lesion is more clearly seen in the standing than in the lying position (panel B).

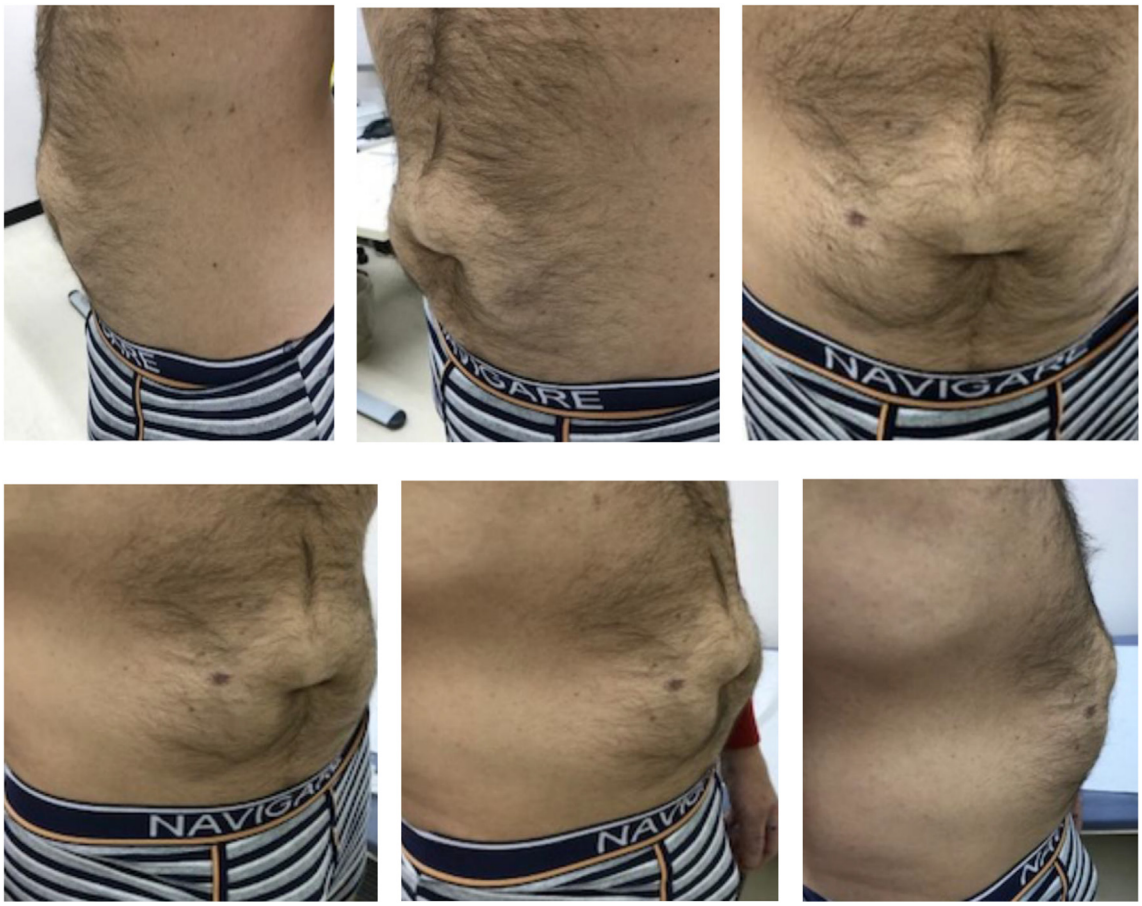


Fig. 4. Patient's rotation from right to left makes LH progressively less visible: the three upper panels show the LH lesion surrounding the navel much more clearly than the three lower panels, where the patient has completed his rotation to the left.
The presence of paraombelical hernia was ruled out by ultrasonography.

6. Conclusion

To make a long story short, we can conclude that the large LH rate variability reported in the literature depends on a series of observer mistakes (or at least inaccurate behaviors); therefore the experience of professionals involved in LH identification, as well as, time devoted to education refreshers and clinical examination by diabetes teams are crucial for efficiently preventing patients from performing insulin injections incorrectly.

From a practical point of view, in addition to:

1) inspecting injection sites through direct and/or skin-tangential light
2) palpating injection sites systematically,
3) repeating this maneuver several times by first palpating with a light touch and subsequently with a stronger one in different directions,
4) performing the pinching maneuver to identify any thickness or texture differences in the skin surrounding injection areas

we suggest health professionals to perform both observation and palpation in the upright and the lying position, as well as, to look at their patients from various view-angles and preferably against a dark background, and ask them to stand up from supine and to slowly turn around.

We are fully aware that our latest comments are highly subjective, despite being supported by comparisons between the above mentioned WD and WS groups, but we strongly feel like suggesting both training and experienced health professionals to exploit light and postural changes to better identify LH lesions. More accurate and long-lasting patient examinations including structured systematic efforts to identify LH lesions will increase diabetes teams' professional competence in the field, and will efficiently prevent technical errors or correct initial educational shortcomings, thereby lowering LH prevalence and thus reducing the risk of metabolic complications and related costs [4,14–18].

Conflicts of interest

The Authors declare no conflicts of interest.

Authorship

SG and FS created the paper and wrote it. GG critically read the paper. All have complied with data collection, critically assessed the results and approved the final text.

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