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Review

Insulin related lipodystrophic lesions and hypoglycemia: Double standards? ☆

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ABSTRACT

Lipohypertrophy (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.

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1. Definition

Lipohypertrophy (LH) is the most common form of LD and is characterized by thickened hard-elastic adipose tissue with large

adipocytes and a dense fibrous texture [2]. Its structure makes insulin release slower and unpredictable [1,3], as documented by studies analyzing the effects of injections performed directly into the nodules as either single shots [3] or euglycemic clamp infusions [4]. Ultrasonography is the gold standard for their identification but is not suited for daily activities [5], so that best clinical practice guidelines suggest to perform a regular and accurate examination of the injection sites instead [6]. Unfortunately, only few scientific studies provide details of the method used for, and of personnel dedicated to LH identification so far, in spite of our publishing papers thoroughly describing both correct

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examination techniques and the need of dedicated and experienced care teams [5]. This might explain why reported LH rates are so different across the large body of literature.

This might easily reflect either widely spread underestimation of the problem or even unawareness of the metabolic consequences of ignored LH lesions.

2. Clinical impact

LH lesions are in fact clinically relevant rather than merely unpleasant to see: they always cause poor metabolic control indeed, along with large glycaemic variability and unexpected/unpredictable episodes of hypoglycaemia (Hypo) [1,3,5,7]. Nevertheless we have to admit that just few authors seem to be interested in the association between LH and Hypo and fully delegate LH management to nurses, might be depending either on little attention to identification of skin lesions *per se* [8] or on problem underestimation.

Unfortunately, unlike some Scientific Societies publishing detailed guidelines on correct injection techniques [9], the Standards of Medical Care from ADA, one of the most authoritative sources of scientific information for diabetes specialists, still fail to devote a specific section to skin complications of incorrect injection habits [10]: this might in fact justify the above mentioned inhomogeneous attitude found within the scientific community.

3. Insulin pharmacokinetics/pharmacodynamics and LH

In fact, based on drug pharmacokinetics and pharmacodynamics it is easy to understand why insulin injections into LH nodules are associated with large glycaemic excursions and poor metabolic control [3,4]. However sudden Hypos unrelated to well expected causes (including errors in hormone dosage or food intake, vomiting, diarrhoea and so on) are slightly harder to explain. One conceivable reason behind them might be the typical fibrous and firm texture [2] allowing LH to act as a *reservoir* being unpredictably emptied into the blood stream after reaching a critical pressure threshold beyond which a massive insulin release occurs.

A clinical case we published quite recently [11] confirm this hypothesis. To our knowledge, it provided the first evidence of fluid collection spots within large abdominal LH nodules accounting for insulin concentrations up to 13-fold those found in blood. This was also clearly reflected by the fact that Hypo rate progressively decreased as lesions recovered and insulin daily dosage requirement went down by about 20% after the adoption of correct injection habits.

A series of studies [1,8,12] related to the topic and focusing on structured therapeutic education lends support to this by showing dramatically improved LH lesions, reduced glycaemic variability and Hypo rate, as well as, lower insulin daily dosage requirement in patients complying with appropriate injection guidelines [6,13,14].

4. Clinical trials and Real life

During the last two decades pharmacologists prompted a number of randomized clinical trials investigating the effects of fast acting and basal insulin analogs and thus providing new therapeutic opportunities for physicians and patients. However, the literature never investigated patient compliance with best injection practice nor even mentioned needle length choice as apart from occasionally reporting on disposable pens devoted to specific insulin analogs. All this clearly shows that therapeutic schemes and insulin preparations get much stronger attention than injection techniques.

LOCAL COMPLICATIONS OF INSULIN INJECTION

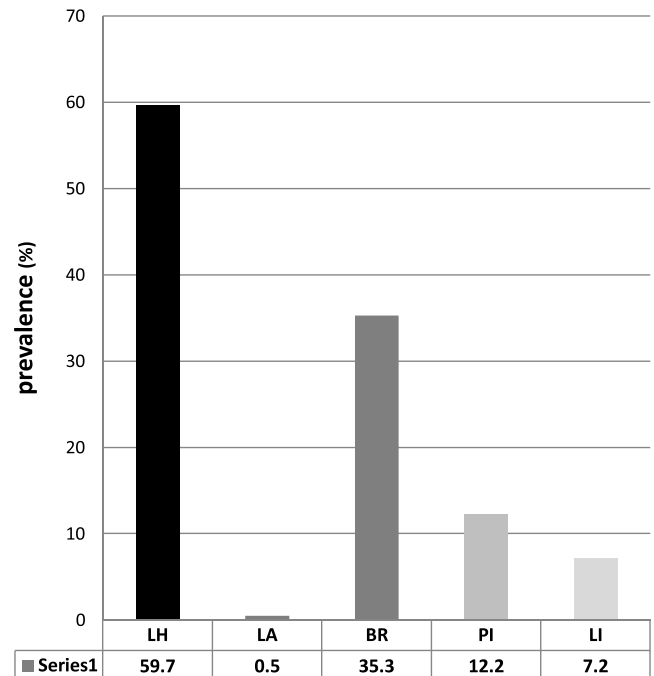


Fig. 1. Local complication of insulin injection in a series of 1085 insulin-treated Type 2 diabetic patients. LH = Lipo hypertrophy, LA = Lipoatrophy, BR = Bruising, PI = pigmentation, LI = Local irritation. Some patient had more than one local complication.

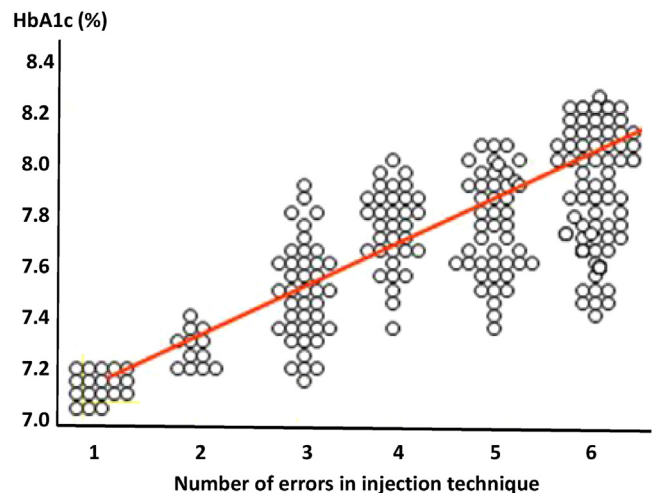


Fig. 2. Relationship between HbA1c levels and errors in injection technique as observed in 160 Type 2 diabetic patients on 3–4 daily insulin injections: ($r = 0.789$, $p < 0.01$). In 62 subjects one or more identified errors were present.

In the interests of completeness of the information, however, we feel like reporting the results of an elegant paper concerning 13 T1DM patients on euglycemic clamp injected insulin lispro into either LH nodules or normal adipose tissue. As expected, drug absorption and effects were blunted and glucose variability was high when insulin was injected into LH lesions but, while postprandial glucose control was fundamentally altered, the risk of Hypo - defined as blood glucose ≤ 50 mg/dL - was reduced [4].

On the contrary, a recent real-life, retrospective analysis of 387 DM patients on 3.7 ± 0.9 Injections/day who had been referred by specialists [9] allowed us to identify an average of 3.3 late postprandial Hypos per week, defined according to ADA definition [10];

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