

Lipohypertrophy: prevalence, clinical consequence, and pathogenesis

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Insulin treatment has many cutaneous alterations and skin-related adverse effect, lipohypertrophy (LH) is the commonest among them.^[1] LH has the definition with a tumor-like lump, visible and touchable, adipose tissue at the site of insulin injection.^[2] It might result from the lipogenic effect of repeated insulin exposure.^[3,4] Injecting insulin into the tissue with LH weakens insulin physiological function, and leads to a resulting excess glucose exposure, glycemic modifiability, and an increased risk of hypoglycemia.^[5] Unfortunately, there is limited information about the pathophysiology of LH in insulin users. As a result, reports of prevalence, clinical consequence, and pathogenesis are needed.

The epidemiological data about LH have shown large differences in prevalence rate. Even in recent 5 years, the prevalence rate of LH in insulin users ranges broadly from 11.1% to 73.4%. In China, the reported prevalence ranges from 53.1% to 73.4%.^[6-8]

The gold standard for the detection of LH is ultrasonic skin scanning, revealing an increased echo of the subcutaneous tissue, and with or without different sizes of the definite nodules in the boundary area.^[9,10] Besides, histopathological biopsy is a reliable method to detect LH, and it can prevent an amyloid mass from being misdiagnosed as LH.^[11] However, for economic and practical reasons, most studies have relied on observing and palpating. The vast difference of prevalence rate could be due to the detection capacity of different inspection staffs.

In fact, the highly variable morphological characteristics of LH in terms of size, texture, and prominence of the skin also make diagnosis difficult [Table 1]. Gentile *et al*^[9] provides a detailed way to identify lesions: the research staff were advised to apply pressure when they noticed a hardening of the skin, confirming first impressions by comparing the thickness of the suspicious area with the thickness of the surrounding area. Then, performing

repeated vertical and horizontal fingertip movements over and around it, pinch maneuvering, and marking it. By repeating the above palpation, most smaller, flatter lesions are easily identified and measured.^[9,10]

A research conducted in Spain recorded severe unknown hypoglycemia in 49.1% of insulin users with LH, whereas in diabetics without LH, this rate was 5.9% to 6.5%.^[12] Patients with LH have an almost seven-fold to 13-fold higher occurrence of glycemic variability compared with person without LH.^[12,13]

In fact, it is easy to understand why injecting insulin into lipohypertrophic tissues is associated with large glycemic excursions and poor metabolic control based on pharmacokinetics and pharmacodynamics. LH is characterized by thickened hard elastic adipose tissue with large adipocytes and dense fibrous texture. Its structural properties make insulin release slower and unpredictable.^[14] A study compared lipohypertrophic tissue and normal adipose tissue and showed that there was a separation of the postmeal blood glucose curves after 30 min leading to significant differences in blood glucose levels from 2 h onwards, and in maximum postprandial blood glucose concentrations.^[5]

Poor glycemic control can increase the risk of various complications of diabetes mellitus, such as cardiovascular disease,^[15,16] diabetic foot,^[17] retinal disease,^[18,19] kidney disease,^[20] and so on. Additionally, patients prefer reutilizing lipohypertrophic areas for injection due to pain reduction. It could increase insulin consumption, medical expenses, and financial burdens on families and communities.^[12,21]

The pathogenesis of insulin-related LH is still unclear.^[12] Among various proposed mechanisms, it seems that LH is a local effect caused by the reaction of adipocytes to the insulin injection. But the susceptibility of LH varies widely, so other immunological factors are possibly involved. A

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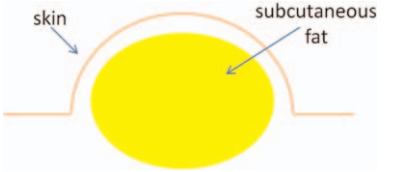


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Table 1: Different types of lipohypertrophy.

Types	Characteristic	Observable	Palpable
	Salient	Easily	Easily
	Almost flat	Hardly	Hardly
	Flat	Not at all	Very hardly

study in Europe showed that the level of anti-insulin antibody had a positive relationship with LH.^[22] Usually, the anti-insulin antibodies are IgG or IgE antibodies. Several factors influence the production of anti-insulin antibodies, such as genetics, the purity of insulin, the source of insulin, insulin species, mode of administration, and so on.^[23]

On the other hand, insulin has an anabolic effect on local adipocytes, promoting the synthesis of fats and proteins; these may cause the occurrence of LH. Notably, patients using regular insulin had a 3.2-fold risk of LH than those using fast insulin for the same average insulin injection frequency.^[3] This observation could be due to the faster absorption from the relatively higher number of insulin monomers contained in the rapid-acting insulin analogs compared with regular insulin.^[3] Due to improved pharmacokinetic actions, rapid-acting insulin analogs, in contrast to conventional insulin, are likely to prevent adipocytes from the lipogenic action.^[24]

Already known risk factors of LH include high body mass index, frequency of needle reuse, failure to alternate injection sites and internal rotations, frequency of daily injections, length of the needle, duration of insulin therapy, high hemoglobin A1c, and patients with hypoglycemia.^[8,12,25,26] Patients' behaviors play a significant role in LH, since patients prefer reusing less painful tissue and more promptly accessible sites.^[9]

Altogether, these mechanisms have a certain impact on the occurrence of LH, but additional research is needed to unravel a clear pathophysiological mechanism of LH in insulin users.

Specific treatment of LH is still unavailable because the pathophysiological mechanism of LH has not been fully understood. Liposuction has been tried as a therapeutic treatment, but it can only alleviate the symptoms.^[27] Proper insulin administration technique, avoiding insulin injection at lipohypertrophic areas, and rotation of injection sites can reduce LH size over time.^[28,29]

In conclusion, prevention and appropriate follow-up should take the first place in the management of these

patients. It is imperative for medical staff to teach patients the correct method of insulin injection during treatment. Not only that, LH should be checked at the injection site as a part of the annual review for insulin users.

Conflicts of interest

None.

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