



Lipohypertrophy at Injection Sites: An Underexamined Cause of Unexplained Glycaemic Variability

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Abstract

Insulin injected into lipohypertrophic tissue is absorbed erratically, and the consequence presents as unexplained glycaemic variability and hypoglycaemia rather than as a skin complaint. Meta-analysis reports pooled odds ratios of 6.98 for unexplained hypoglycaemia, 6.65 for hypoglycaemia overall and 5.24 for glycaemic variability where lipohypertrophy is present, with HbA1c higher by 0.55 percentage points and daily insulin consumption by 7.68 units. Prevalence in an outpatient cohort of 430 was 64.4 per cent, and site rotation was the discriminating factor: only 5 per cent of those rotating correctly were affected, while 98 per cent of those affected did not rotate or rotated incorrectly. Detection depends on method, with ultrasound identifying lesions in over 80 per cent of cases and palpation missing non-palpable disease. The examination is recommended six-monthly for the first two years of insulin therapy and is not routinely performed.

Keywords: Lipohypertrophy; Injection technique; Glycaemic variability; Hypoglycaemia; Site rotation

Introduction

Repeated insulin exposure at a single site has a lipogenic effect on subcutaneous tissue, and the fat cells enlarge and proliferate to form thickened tissue or palpable lumps [1,2]. Insulin delivered into that tissue is absorbed slowly and unpredictably, because the affected area has altered architecture and reduced vascularity [3,4].

The clinical presentation is therefore not dermatological. It appears as unexplained glucose variability, hypoglycaemia that makes no sense against the recorded dose, and rising insulin requirement [5,6]. This short communication sets out what has been measured and why the condition is missed.

Rotation is the discriminating factor: In the same outpatient cohort, only 5 per cent of those who rotated sites correctly were affected, while 98 per cent of those with lipohypertrophy either did not rotate or rotated incorrectly (Figure 1) [7]. Risk also rose with needle reuse, significantly so beyond five uses [7]. An international consensus panel identified inadequate rotation as the strongest modifiable risk factor [9].

Observations

How common it is: In an outpatient cohort of 430 people injecting insulin, examined by a diabetes nurse after completing a questionnaire on injection technique, 64.4 per cent had lipohypertrophy [7]. A paediatric cross-sectional study of 212 patients, assessed by inspection and palpation, reported a prevalence of 44.3 per cent, with lipoatrophy in two patients [8].

What it does to control: Meta-analysis reported that people with lipohypertrophy were more likely to experience unexplained hypoglycaemia, with a pooled odds ratio of 6.98 (95% CI 3.30 to 14.77), hypoglycaemia overall at 6.65 (1.37 to 32.36) and glycaemic variability at 5.24 (2.68 to 10.23) (Figure 2). HbA1c was higher by 0.55 percentage points (0.23 to 0.87) and daily insulin consumption by 7.68 units (5.31 to 10.06) [10].

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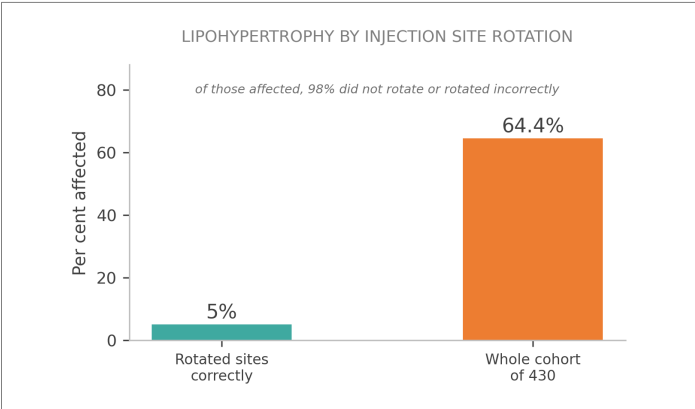


Figure 1: Lipohypertrophy by injection site rotation in a cohort of 430 [7]

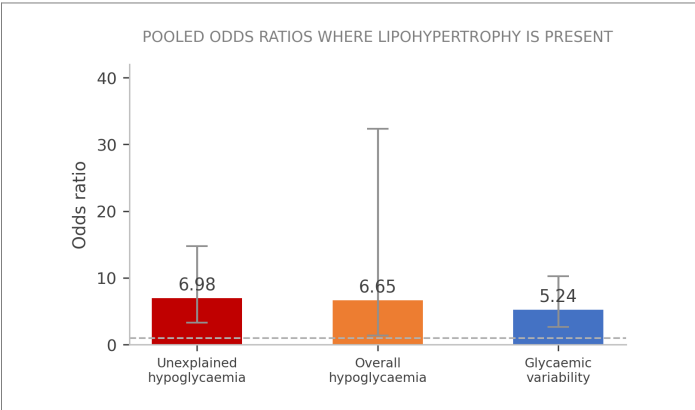


Figure 2: Pooled odds ratios where lipohypertrophy is present [10]

Consistency across cohorts: In the outpatient study, 39.1 per cent of those with lipohypertrophy reported unexplained hypoglycaemia and 49.1 per cent glycaemic variability, and total daily insulin averaged 56 against 41 units in those without [7]. In the paediatric cohort, coefficient of variation and standard deviation of glucose differed significantly between those with and without the condition [8].

Measure	Reported difference
Unexplained hypoglycaemia	Odds ratio 6.98 (3.30 to 14.77) [10]
Glycaemic variability	Odds ratio 5.24 (2.68 to 10.23) [10]
HbA1c	Higher by 0.55 points (0.23 to 0.87) [10]
Daily insulin	Higher by 7.68 units (5.31 to 10.06) [10]
Daily insulin, single cohort	56 against 41 units [7]

Table 1: Reported differences between people with and without lipohypertrophy

Detection depends on method: Ultrasound is more sensitive than palpation, and ultrasound-verified lipohypertrophy has been detected in more than 80 per cent of cases examined (Figure 3) [11,12]. Non-palpable disease is difficult to identify at the bedside, and systematic review has noted limited information comparing the sensitivity of the available techniques [12,13]. Consensus recommendations propose systematic examination of injection sites every six months during the first two years of insulin therapy and annually thereafter [9].

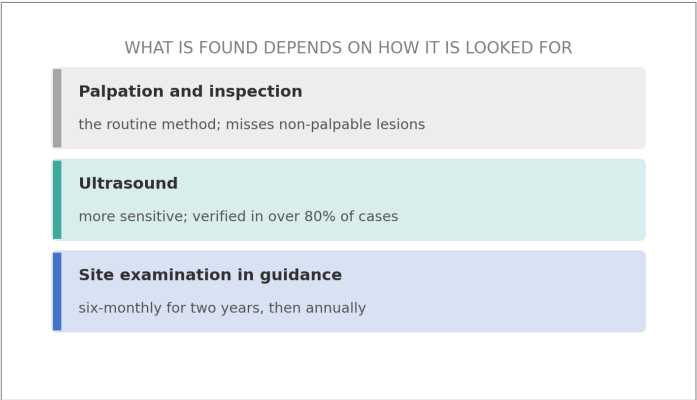


Figure 3: Detection of lipohypertrophy by method [9,11,12]

Discussion

The reason this matters clinically is that the presentation and the cause sit in different specialties. A patient with erratic readings and hypoglycaemia that does not match the dose prompts a review of the regimen, the carbohydrate estimate or the monitoring, and the injection sites are frequently not examined at all [9,13]. The pooled odds ratio of 6.98 for unexplained hypoglycaemia suggests that where the hypoglycaemia is genuinely unexplained, the sites are among the more productive places to look [10].

Two things complicate acting on this. The first is detection: prevalence figures of 44, 64 and over 80 per cent come from palpation, examination by a trained nurse, and ultrasound respectively, so what is found depends substantially on how hard one looks [7,8,11]. Palpation performed casually will underestimate it.

The second is what follows a positive finding. Absorption from unaffected tissue is faster and more complete, so moving injections to a healthy site without reducing the dose carries a risk of significant hypoglycaemia [11,14]. Identifying lipohypertrophy therefore obliges a dose review rather than simply an instruction to change sites, and that is a clinical decision for the treating team rather than an educational message.

A limitation applies to all of this. The studies are cross-sectional, and the direction of the association is not established by them [8,10,15]. Poor control might plausibly lead to more frequent injection into fewer convenient sites, rather than the lesions causing the poor control, and the observed relationship is compatible with both. The pharmacokinetic evidence that absorption from affected tissue is blunted and variable is what makes the causal reading plausible, and that evidence is separate from the epidemiological association [3,4].

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Limitations

These are observations from cross-sectional studies of varying size and method. Prevalence estimates are not comparable across studies because detection technique differs [7,8,11]. Hypoglycaemia and variability are frequently self-reported [7,10]. The meta-analysis pools heterogeneous cohorts and its confidence intervals are wide, particularly for overall hypoglycaemia [10]. And no randomised trial has tested whether systematic site examination improves glycaemic outcomes, so the recommendation rests on the strength of the association and the low cost of looking [9,13].

Conclusion

Lipohypertrophy is present in a substantial proportion of people injecting insulin, and where it is present the odds of unexplained hypoglycaemia are roughly sevenfold and of glycaemic variability fivefold. Correct site rotation is the discriminating factor, with 5 per cent of correct rotators affected against 64.4 per cent of the whole cohort. The examination is recommended six-monthly for the first two years and is not routinely done, which means an inspection costing a few minutes sits upstream of a common and otherwise puzzling clinical problem. A positive finding obliges a dose review rather than only a change of site.

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Conflict of Interest

The authors declare no competing interests.

Ethics Statement

This article reviews previously published studies only. No new patient data were collected, so ethical approval was not required.

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