The prevalence of lipohypertrophy and its associated factors among Saudi patients with type 2 diabetes mellitus

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Abstract

Objectives: We conducted this study to establish the prevalence and associated risk factors of lipohypertrophy (LH) in patients with type 2 diabetes mellitus (T2DM) who are on insulin therapy in the Kingdom of Saudi Arabia (KSA).

Methods: This multicenter, cross-sectional study was executed at primary care clinics in King Saud University Medical City and Prince Mohammed Bin Abdulaziz Hospital in Riyadh KSA from May 2017 to October 2017. All adult patients over 18 years old with T2DM who had been treated with insulin via either a syringe or pen for at least two years were physically examined for LH.

Results: A 39.7% prevalence of LH was found in our study cohort of which as many as 57.5% patients were found to be in LH grade 1, 33.75% grade 2, and 8.75% grade 3. LH was detected in 68.8% patients who used different sites for every injection and in 63.7% (p = 0.182) of patients who had injected more than 60 units per day (p < 0.0001). Overall logistic regression analysis showed that the patients who used alcohol swabs were 2.6 times more likely to develop LH. Interestingly, the patients who used more than 60 units of insulin per day were 0.362 times more likely to develop LH.

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Conclusions: Lipohypertrophy is a complication common among patients with T2DM in KSA. It is incumbent upon healthcare providers to raise awareness about LH and to provide extensive education about correct insulin administration among patients with T2DM on insulin therapy.

Keywords: Insulin; KSA; Lipohypertrophy; Prevalence; Type 2 diabetes

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Introduction

It has been estimated that 38% of patients will be prescribed insulin treatment 10 years after they are diagnosed with type 2 diabetes mellitus (T2DM).1 Proper insulin administration is essential to ensure optimal insulin absorption and function.2 Unfortunately, most patients either receive substandard insulin education or do not follow their healthcare provider’s instructions with regard to administering insulin.2,3 Lipohypertrophy (LH) is defined as an accumulation of fat under the subcutaneous insulin injection site.1 It is the most common complication associated with insulin administration.4 Injecting insulin into lipodystrophied sites leads to decreased insulin absorption, which ultimately results in poor glycaemic control.2 Unfortunately, most patients prefer to inject insulin into areas associated with LH because of reduced pain compared to normal injection sites.2 Some factors associated with the development of LH include needle length, needle gauge, rotation of injection sites, frequency of needle changes, and body mass index (BMI).4

Several studies have been conducted to determine the worldwide prevalence of LH in patients with T2DM. The prevalence of LH in Jordan, Turkey, Spain, the United Kingdom, Germany, and China is 37.3% 48.8%, 56%, 28%, and 3.6%, 53.1, respectively.1,2,4,5,18 Deng and colleagues conducted a recent systematic review and meta-analysis of the prevalence of LH in patients with diabetes, including type 1 diabetes mellitus (T1DM), T2DM, and mixed diabetes treated with insulin.7 They reported that most studies have been conducted in Asian countries and Europe and that the prevalence of LH in Asian countries was higher than that of European countries.

Specifically, only one study has been published in the Kingdom of Saudi Arabia (KSA) to investigate the prevalence of LH in patients with T1DM, and in this study, Al Hayek et al. reported a 47.7% prevalence of LH among T1DM patients.4 Currently, there are no published studies that have been conducted to investigate the prevalence of LH in patients with T2DM in KSA. Therefore, the objective of this study was to establish the prevalence of LH in patients with T2DM in KSA who were taking insulin treatment and determine the associated risk factors.

Materials and Methods

Study design and settings

A multicenter, cross-sectional study was conducted from May to October 2017 among adult patients with T2DM who were undergoing insulin therapy in primary care clinics at King Saud University Medical City (KSUMC) and Prince Mohammed Bin Abdulaziz Hospital in Riyadh, KSA. The inclusion criteria for this study was adult patients aged >18 years with T2DM who were being treated with insulin, using either syringes or pens, for at least two years. Patients were excluded if they were not using insulin, pregnant or lactating, or had been diagnosed with T1DM.

We calculated the sample size based on the results of the pilot study. Since 15% of the participants with type 2 diabetes in the pilot study had LH, with a power of 80% and a 5% margin of error, we calculated the sample size required 196 participants. Allowing for a non-response rate of 30%, the survey questionnaire was distributed among 254 participants.

Study tools and data collection

An extensive review of the published literature was conducted related to the assessment of LH among patients with T2DM on insulin therapy. The questionnaire used in this study was a modified version of the survey applied in other studies assessing insulin injection administration.2,7 The questionnaire was translated into Arabic by two independent and certified translators and back-translated into English by a further two independent and certified translators. To ensure content and face validity, two diabetologist researchers familiar with survey development assessed the questionnaire for appropriateness, accuracy, and relevance. The survey was piloted among 20 patients with diabetes at KSUMC. Glycated haemoglobin (HbA1c) values <7% were classified as controlled.7,8 BMI was categorized into three groups: 18.5–24.9 kg/m² (normal), 25–29.9 kg/m² (overweight), and ≥30 kg/m² (obese). The Cronbach’s alpha value, used as a measure of reliability, was 0.657. A simple random sampling technique was used to collect the data from the sampling frame of the population. The principal investigator was responsible for data collection and was unaware of the LH status of the patients at study entry.

Measurement of lipohypertrophy

The presence of LH was examined by inspecting and palpating each insulin injection site. The examination was performed only by the primary investigator who had been trained in Diabetes Clinics at King Khalid University Hospital for two months prior to data collection. Each patient was given the study questionnaire and examined immediately after completion. Palpable LH or a noticeable mass at the insulin injection sites indicated the presence of LH, and the absence of LH indicated a normal injection site.7 LH grades were defined as follows: grade 0, no change; grade 1, visible hypertrophy of fat tissue, but with normal consistency on
palpation; grade 2, intensive fat tissue thickening, but with firm consistency; and grade 3, lipoatrophy.\textsuperscript{4,6}

Statistical analysis

Data were entered using Microsoft Excel and analyzed using the Statistical Package for the Social Sciences (SPSS) version 21 software (SPSS Inc., Chicago, IL, USA). A chi-squared test was used to assess factors that influenced the development of LH. Risk factors found to be statistically significant were evaluated by logistic regression analysis. $P$-values $<0.05$ were considered statistically significant.

Ethical consideration

The study concept and objectives were explained to patients before obtaining their written informed consent. Ethical approval was obtained from the King Saud University College of Medicine Institutional Review Board, and the study was conducted according to the Strengthening the Reporting of Observational Studies in Epidemiology statement.\textsuperscript{9}

Results

Patient demographics

A total of 202 patients diagnosed with T2DM and taking insulin therapy completed the survey with a 79.5% response rate. The majority of participants were women (55.9%). The mean age, duration of diabetes, and duration of insulin therapy was 58.5 years, 16.9 years, and 8.5 years, respectively. Using HbA1c as the criteria for glycaemic control, 91.1% of the study participants had uncontrolled blood glucose levels (Table 1).

Injection technique related risk factors

The possible risk factors influencing LH are presented in Table 2. Approximately, 73% of the study participants used insulin pens instead of vials and syringes. In addition, a high percentage (73.8%) of patients reported cleaning their skin with a disinfectant, such as alcohol swabs, before each injection. The primary types of insulin used by patients were basal-bolus insulin regimens (38.3%) followed by premixed insulin (32.8%).

Relationship between risk factors and lipohypertrophy

There was a 39.7% prevalence of LH in our study. LH was detected in 73.8% of obese patients and 68.8% of patients who used a different site at every injection. However, there was no statistically significant relationship between either BMI or changing the injection site and the development of LH. Approximately, 83.8% of patients who used alcohol swabs had LH, and the use of alcohol swabs was found to be positively associated with the development of LH (Table 3). Patients were further divided into two subgroups aged $\leq$60 years. The percentage of patients in the $\leq$60 years age group who developed LH was 55%; however, none of the demographic characteristics in our study were significantly associated with LH (Table 4).

| Table 1: Patient demographics. |
|--------------------------------|
| Characteristics | N (%) | Mean(SD) |
| Continuous characteristics (mean $\pm$ SD) |
| Age $<60$ yrs | 103 | 51.0 |
| $\geq60$ yrs | 99 | 49.0 |
| Duration of diabetes $\leq5$ y | 15 | 7.4 |
| 6–10 y | 49 | 24.3 |
| 11–15 y | 32 | 15.8 |
| $>15$ y | 106 | 52.5 |
| Duration of insulin treatment $\leq5$ y | 80 | 39.6 |
| 6–10 y | 70 | 34.7 |
| 11–15 y | 25 | 12.4 |
| $>15$ y | 27 | 13.4 |
| HbA1c $\leq7.0$ | 18 | 8.9 |
| $>7.0$ | 184 | 91.1 |
| Total insulin daily dose $<60$ unit | 104 | 51.5 |
| $\geq60$ unit | 98 | 48.5 |
| BMI Normal | 20 | 9.9 |
| Overweight | 48 | 23.8 |
| Obese | 134 | 66.3 |
| Categorical characteristics, n (%) |
| Gender Male | 89 | 44.1 |
| Female | 113 | 55.9 |
| Education level No school | 57 | 28.2 |
| attended Primary school | 44 | 21.8 |
| Secondary | 24 | 11.9 |
| school Tertiary school | 38 | 18.8 |
| University or college | 39 | 19.3 |
| Location Riyadh | 158 | 78.2 |
| Outside Riyadh | 44 | 21.8 |
| Health care canter KSUMC | 106 | 52.5 |
| Prince | 96 | 47.5 |
| Mohammed Bin Abdulaziz hospital | |
| Monthly income $<5000$ | 79 | 39.1 |
| $5000–10,000$ | 52 | 25.7 |
| 10,001–15,000 | 45 | 22.3 |
| $>15,000$ | 26 | 12.9 |
| Marital status Single | 2 | 1.0 |
| Married | 155 | 77.1 |
| Divorced | 30 | 14.9 |
| Widowed | 14 | 7.0 |

Abbreviations: N: number; SD: standard deviation; KSUMC: King Saud University Medical City.
Table 2: Risk factors influencing LH.

| Characteristics                | LH status | N   | (%) |
|--------------------------------|-----------|-----|-----|
|                               | Present   | 80  | 39.7|
|                               | Grade 1   | 46  | 22.8|
|                               | Grade 2   | 27  | 13.4|
|                               | Grade 3   | 7   | 3.5 |
|                               | Not present| 122 | 60.3|
| Device used                    | Pen       | 147 | 72.8|
|                               | Syringe   | 55  | 27.2|
| Total daily injections         | 1         | 39  | 19.3|
|                               | 2         | 88  | 43.6|
|                               | 3         | 18  | 9.9 |
|                               | 4         | 53  | 26.2|
|                               | 5         | 4   | 2.0 |
| Needle length                  | 4 mm      | 124 | 61.4|
|                               | 5 mm      | 16  | 7.9 |
|                               | 6 mm      | 5   | 2.5 |
|                               | 8 mm      | 5   | 2.5 |
|                               | Don’t know| 52  | 25.7|
| Frequently changed needles/syringes | At every injection | 120 | 60.3|
|                               | At every 2–3 injections | 38  | 19.1|
|                               | At every 4–5 injections | 30  | 15.1|
|                               | When cartridge finished | 11  | 5.5 |
| Changing site of injections   | A different site at every injection | 128 | 63.7|
|                               | A week at each site | 24  | 11.9|
|                               | Haphazardly | 28  | 13.9|
|                               | Using only one site | 21  | 10.4|
| Injection site used           | Abdomen   | 48  | 23.8|
|                               | Thighs    | 94  | 46.5|
|                               | Buttocks  | 4   | 2.0 |
|                               | Arm       | 56  | 27.7|
| Type of insulin               | Basal-bolus| 77  | 38.3|
|                               | Basal insulin alone | 25  | 12.4|
|                               | Premixed regular insulin | 66  | 32.8|
|                               | Premixed insulin analogue | 33  | 16.4|
| BMI                           | Normal    | 20  | 9.9 |
|                               | Overweight | 48  | 23.8|
|                               | Obese     | 134 | 66.3|
| Does the patient have swelling or lumps under the skin at the injection sites? | Yes | 62  | 30.8|
|                               | No        | 139 | 69.2|
| Does the patient inject into these swellings or lumps? | Always | 4   | 6.8 |
|                               | Sometimes | 27  | 45.8|
|                               | Never     | 28  | 47.5|
| Does the patient clean their skin with disinfectant (e.g. an alcohol swab) before injecting? | Yes | 149 | 73.8|
|                               | No        | 53  | 26.2|
| Injecting insulin             | Vertical  | 158 | 78.2|
|                               | Horizontal| 36  | 17.8|
|                               | Haphazardly | 8   | 4.0 |

Abbreviation: N: number.

Table 3: The association between factors influencing LH and the status of LH.

| Characteristics | LH status | Total | P-valuea |
|-----------------|-----------|-------|----------|
|                 | Present   | Not Present | N (%) | N (%) |       |
| Device used     | Pen       | 53 (66.3%) | 94 (77.0%) | 147 | 0.092a |
|                               | Syringe   | 27 (33.8%) | 28 (23.0%) | 55  | (27.2%) |
| Total daily injections | 1         | 7 (8.8%) | 32 (26.2%) | 39  | (19.3%) |
|                               | 2         | 42 (52.5%) | 46 (37.7%) | 88  | (43.6%) |
|                               | 3         | 7 (8.8%) | 11 (9.0%) | 18  | (8.9%) |
|                               | 4         | 24 (30.0%) | 29 (23.8%) | 53  | (26.2%) |
|                               | 5         | 0 (0%) | 4 (3.3%) | 4 (2.0%) |
| Needles/syringes | At every injection | 120 | 60.3|
|                               | At every 2–3 injections | 38  | 19.1|
|                               | At every 4–5 injections | 30  | 15.1|
|                               | When cartridge finished | 11  | 5.5 |
| Injection site used         | A different site at every injection | 128 | 63.7|
|                               | A week at each site | 24  | 11.9|
|                               | Haphazardly | 28  | 13.9|
|                               | Using only one site | 21  | 10.4|
| Type of insulin            | Basal-bolus| 28 (35.0%) | 49 (40.5%) | 77  | 0.184 |
|                               | Basal insulin alone | 31 (38.8%) | 44 (36.1%) | 75  | (37.1%) |
|                               | Premixed regular insulin | 31 (38.8%) | 44 (36.1%) | 75  | (37.1%) |
|                               | Premixed insulin analogue | 19 (23.8%) | 33 (27.0%) | 52  | (25.7%) |

(continued on next page)
### Table 4: The association between patient demographics and the status of LH.

| Characteristics | LH status | Total N (%) | P-value |
|-----------------|-----------|-------------|---------|
|                 | Present N (%) | Not Present N (%) |     |
| Basal insulin alone | 6 (7.5%) | 19 (15.7%) | 25 | 0.203<sup>a</sup> |
| Premixed regular insulin | 31 (38.8%) | 35 (28.9%) | 66 | (32.8%) |
| Premixed insulin analogue | 15 (18.8%) | 18 (14.9%) | 33 | (16.4%) |
| Duration of diabetes (years) | 60 yrs | 44 | 170 | 0.043<sup>a</sup> |
| Age | 57.56 (10.6) | 59.16 (11.7) | 58.53 (11.3) | 0.324<sup>a</sup> |
| Education level | No school | 22 | 35 | 0.150 |
| University or college | 12 | 27 | 39 | 0.052 |
| Gender | Male | 59 | 99 | 0.128 |
| Female | 50 | 63 | 113 | (56.3%) (50.0%) (52.5%) |
| Health care centre | KSUMC | 45 | 61 | 106 | 0.384 |
| Location | Riyadh | 57 | 101 | 158 | 0.0001<sup>b</sup> |
| Outside Riyadh | 23 | 21 | 44 | 0.997 |

<sup>a</sup> Chi-squared test was used in the analysis.

<sup>b</sup> Statistically significant.
In this study it was found that the application of alcohol swabs at the injection site increased the patient’s risk for developing LH. Among those who used alcohol swabs at the injection site, 83.8% of patients developed LH, which is inconsistent with those reported by Husain et al. and Tandon et al., who found that alcohol swabs have no significant effect on LH or the prevention of infection. In addition, the highest proportion of patients with LH in their studies had a duration of insulin therapy of 6–13 years (35%), whereas half of our patients had been using insulin therapy for >15 years. Moreover, the insulin dose in this study was considerably higher than that reported by Blanco and colleagues (26.9%). Therefore, further research is needed to determine whether there are other contributing factors influencing the association between LH and use of alcohol swabs at the injection site.

As for the effects of insulin dosage, we found that a total daily dosage (TDD) of >60 units significantly increased the risk of developing LH, as 63% of patients who received a higher dosage developed LH. This relationship was consistent with the findings of Blanco et al. and Ji et al. who observed that TDDs of >62 and 38 units, respectively, significantly increased the risk of T2DM patients developing LH. The relationship between TDD and LH can be attributed to the fact that insulin increases the effects of lipogenesis on the skin, and insulin can act as an insulin-like growth factor. Moreover, patients with T2DM tend to increase insulin dosage due to weight gain, insulin resistance, and repeatedly using sites with LH that they consider to be less painful.

We found no statistically significant relationship between the duration of insulin therapy and the development of LH, which is contrary to the studies conducted by Hauner et al. and Strauss et al. both of which observed a significant relationship between the duration of insulin therapy and the development of LH. We also found that rotating the insulin injection site had no significant relationship with LH development. In our study, 63.7% of patients used a different site at every injection, 11.9% changed the site every week, and 10% used the same injection site each time. The most common site of injection used by our study population was the thigh, followed by the abdomen. Hajheydari et al. and Nasser et al. also found no significant relationship between rotation of the insulin injection sites and LH development. Hajheydari et al. attributed this lack of relationship to the fact that patients randomly rotate injection sites. It is worth noting that Chowdhury et al. reported that rotating insulin injection sites provides better blood glucose control and improves LH. Furthermore, site rotation also increases insulin absorption, resulting in an overall reduction of insulin doses by 2–4 units.

There was no significant association between needle changes and the development of LH. This is consistent with the findings reported by Nasser and colleagues. In contrast, it was found that having fewer needle changes was associated with a higher risk of developing LH in other previous studies. A possible explanation for the insignificant

## Discussion

The prevalence of LH in our study was found to be 39.7%, which is consistent with the prevalence rates of 36.8%, 37.3%, and 48.8% reported by Nasser et al. We found that the risk factors pertaining to alcohol swab use and total daily insulin dosage were the only factors that were significantly associated with the development of LH. To the best of our knowledge, this is the first published study regarding the prevalence of LH in patients with T2DM in the Saudi population.

### Table 4 (continued)

| Characteristics | LH status | Total N (%) | P-value |
|-----------------|-----------|-------------|---------|
|                 | Present N (%) | Not Present N (%) | |
| Prince Mohammed Bin Abdulaziz Hospital | 35 (43.8%) | 61 (50.0%) | 96 (47.5%) |
| Marital status |            |             |         |
| Single          | 0 (0%)    | 2 (1.7%)    | 2 (1.0%) | 0.134 |
| Married         | 65 (81.3%) | 90 (74.4%)  | 155 (77.1%) |
| Divorced        | 13 (16.3%) | 17 (14.0%)  | 30 (13.1%) |
| Widowed         | 2 (2.5%)  | 12 (9.9%)   | 14 (7.0%) |

* a The Student’s t-test was used in the analysis of continuous variables.
* b Chi-squared test was used in the analysis for categorical variables.

### Table 5: The logistic regression analysis.

| Variables | Odds Ratio | P-value |
|-----------|------------|---------|
| Cleaned the skin with a disinfectant | 2.659 | 0.009 |
| Total insulin daily dose | 0.362 | 0.002 |

Regarding the effects of insulin dosages, we found that 63.7% of patients who received >60 units of insulin per day had developed LH (p < 0.0001). We found no significant relationship between the duration of insulin therapy or uncontrolled diabetes and the development of LH (Table 4). Multivariate logistic regression analysis was used to identify risk factors independently related to LH. Participants who used alcohol swabs and injected <60 units of insulin per day were 2.6 times more and 0.362 times less likely to develop LH, respectively (Table 5).
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Conclusions

Lipohypertrophy is a common complication among patients with T2DM in KSA. Further studies are needed to examine the relationship between LH and its associated risk factors. Additional recommendations for future studies include enrolling a larger sample size, recruiting patients from various cities throughout KSA, and ensuring participation from rural and underserved areas.

Source of funding

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Conflict of interest

The authors have no conflict of interest to declare.

Ethical approval

The study was approved by the king Saud University College of medicine ethics committee. Data were anonymized by removing any personal information for the purpose of confidentiality.

Authors contributions

ANA and IS conceived and designed the study, conducted research, THA and MAB provided research materials, and collected and organized data. ANA analyzed and interpreted data. THA and SW wrote initial and final draft of article, and provided logistic support. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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relationship found is that 57% of patients in our study and 89.5% in that of Nasser et al. reported that they do not reuse needles. Blanco et al., Strauss et al., and Vardar et al. reported that 44%, 40.9%, and 34.5% of their patients did not reuse needles, respectively.

As for the effects on glycaemic control, we found no statistically significant relationship between HbA1c level and the development of LH. An estimated 91% of patients in our study were found to have uncontrolled HbA1c levels. The lack of a significant relationship between glycaemic control and LH is consistent with the findings of McNally et al. and Hauner et al. They both attributed the significance to the effects of poor insulin absorption, which can lead to the formation of fibrous tissue in sites with LH and consequently, instabilities in blood glucose levels (i.e. fluctuations between hyper- and hypoglycaemia). However, a significant association between poor glycaemic control and LH has been reported in some previous studies. 

No statistically significant associations between any of the remaining risk factors considered in our study and LH were found (e.g. BMI, needle length, insulin education, and gender). These results are consistent with previous studies by Vardar et al., McNally et al., and Strauss et al. There are several limitations in our study that need to be overcome in future research to achieve more generalizable findings. First, patient examinations for LH were conducted using physical inspection and palpation. Unfortunately, this can lead to variations in diagnosis among practitioners. This can be alleviated by considering the low cost-effective alternative of using an ultrasound skin scan, which is the gold standard for LH diagnosis. Second, the study participants were all patients from tertiary hospital primary care clinics and patients in these settings are more likely to have multiple comorbidities and access to the healthcare system. Such biases can be eliminated by conducting research at primary healthcare centres in rural and urban areas. The third limitation is the relatively small sample size of 202 patients in this study. In a recent systematic review and meta-analysis, the majority of published literature has included >200 participants. Furthermore, studies with <200 participants tended to have a higher prevalence of LH. Although, the sample size of 202 patients is numerically greater than 200, a larger patient population may prevent any unnecessary ambiguity.

Recommendations derived from this study include an emphasis on health practitioners to regularly examine patients taking insulin for the development of LH. The results also stress the necessity of the involvement of a multidisciplinary team to overcome the increasing incidence of LH through continuous education and follow-up. Extensive education about the complications of inappropriate insulin injection technique is prudent so as to limit the development of LH. Furthermore, patients should be instructed how to identify LH. On the international level, consensus guidance is needed regarding the classification of LH for non-ultrasound identification of LH.
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