Prevalence of lipohypertrophy in insulin-treated diabetes patients: A systematic review and meta-analysis

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Keywords
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ABSTRACT
Aims/Introduction: Insulin-treated diabetes patients are at high risk for lipohypertrophy (LH), but this clinical problem has been overlooked by some medical professionals. In addition, studies differed from each other significantly in regard to the prevalence of LH. The present systematic review aimed to determine pooled prevalence levels of LH among insulin-injecting diabetes patients.

Materials and Methods: Four electronic databases (PubMed, EMBASE, The Cochrane Library and Scopus) were searched for eligible studies from their inception until April 2017, and reference lists were searched manually to identify additional studies. Studies containing data on LH in patients with diabetes mellitus were included. Meta-analysis was carried out with a random effects model.

Results: A total of 26 studies with a total of 12,493 participants met the inclusion criteria. Meta-analysis showed that the pooled prevalence of LH was 38% (95% confidence interval [CI] 29–46%, I² = 99.1%). The main influence on LH was the type of diabetes mellitus. The pooled prevalence of LH among patients with type 2 diabetes mellitus was higher than patients with type 1 diabetes mellitus (49%, 95% CI 23–74% vs 34%, 95% CI 19–49%). The pooled prevalence of LH of studies involving a mixed type of diabetes mellitus was 37% (95% CI 25–48%, I² = 98.3%).

Conclusion: The prevalence of LH was high in insulin-treated diabetes patients. It showed that diabetes nurses should screen for LH regularly in their patients, and teach them how to prevent LH in their daily management of diabetes mellitus.

INTRODUCTION
Diabetes mellitus has been an epidemic worldwide, the number of patients with diabetes mellitus all over the world is estimated to reach 642 million by 20401. Patients with type 1 diabetes mellitus rely on exogenous insulin whether through continuous subcutaneous insulin infusion or multiple daily insulin injections to help control their blood glucose level. In addition, more and more individuals with type 2 diabetes mellitus start to use insulin because of failure of oral hypoglycemic medications and recommendations from updated guidelines2. Lipohypertrophy (LH) is a common complication of insulin therapy. It has been reported that patients with LH have an almost sixfold higher occurrence of unexplained hypoglycemia compared with patients without LH, and sevenfold higher occurrence of glycemic variability3. Suboptimal glycemic control also increases the risk of cardiovascular disease4, amputation5, retinal diseases6, kidney disease7 and a range of other diseases, as diabetes mellitus can affect multiple organs. Furthermore, LH can increase economic burden, as diabetes patients with LH consume more insulin8. As a consequence, it is crucial to discern LH from normal skin in diabetes patients through credible methods during their usual follow-up visits, and give them some advice from professionals’ perspective. However, present epidemiological data showed that the prevalence of LH in people with diabetes mellitus ranged widely from 1.9% to 73.4% in different studies9,10. Various factors accounted for this vast difference, including study quality, not using the LH detection
gold standard and the detection capacity of diverse screening staff involved across studies. In order to inform efforts to prevent, treat and identify influencing factors of LH among diabetes patients, dependable estimates of LH prevalence are required. To our knowledge, no systematic review and meta-analysis has been found that quantified the prevalence of LH in patients with diabetes mellitus. The present systematic review, therefore, set out to establish pooled prevalence levels of LH among patients with diabetes mellitus, and to investigate the impacts of study variables on prevalence estimates.

METHODS

Literature search
We searched four electronic data repositories (PubMed, EMBASE, The Cochrane Library and Scopus), and the main search terms were: “diabetes,” “diabetes mellitus,” “lipohypertrophy,” “insulin lipohypertrophy,” “subcutaneous induration,” “endermic induration” and “subcutaneous nodules.” The detailed search strategy is shown in Appendix S1. The search was limited to papers written in English published from the above databases’ inception to April 2017. We also screened the reference lists of retrieved publications, and consulted experts in the field with the purpose of identifying relevant publications reporting the prevalence of LH among diabetes patients.

Study selection
Two authors independently searched four electronic databases, and browsed titles and read abstracts to decide whether the full text should be examined according to the established inclusion and exclusion criteria. Disagreement was resolved by discussing with a third party. Agreement between reviewers in relation to study relevancy was assessed using Cohen’s kappa. We included articles that fulfilled the following criteria: (i) cross-sectional design, baseline cross-sectional data from a longitudinal study or baseline cross-sectional data from a trial, before random allocation; (ii) detected LH by careful examination (at least observation and palpation), studies involving self-report LH prevalence by patients were also included if the sample size was more than 500; (iii) participants were insulin-treated patients with type 1 diabetes mellitus or type 2 diabetes mellitus. We excluded the following studies: commentaries, review articles, case reports, letters to the editor, studies in languages other than English, and studies with participants who did not have diabetes or were pregnant.

Data extraction
Two investigators extracted the data independently using a specific extraction form. The extracted data included the name of the first author, year of study publication, country, sample size, percentage of male participants, mean age of participants, number of participants with type1 diabetes mellitus/type 2 diabetes mellitus, mean diabetes mellitus duration, mean insulin treatment duration, reported prevalence of LH and detection methods of LH. If there were multiple papers from longitudinal or cohort studies, publications were included according to their epidemiological quality.

Figure 1 | Flowchart of literature research. LH, lipohypertrophy.
| Study ID    | Country                        | Sample size | Male (% | Age, years (mean ± SD) | T1DM/T2DM | DM duration, years (mean ± SD) | Insulin treatment duration (years) | Prevalence of LH (%) | Methods for detection of LH |
|------------|--------------------------------|-------------|---------|------------------------|-----------|-----------------------------|-----------------------------------|---------------------|---------------------------|
| McNally    | UK 1988                         | 281         | 53.7    | Mean: 45.0             |            |                             | Mean: 11.0                        | 27.1                | OAP by physicians          |
| Hauner     | Germany                         | 270         | 44.1    | Mean: 37.0             | Range: 15.0–22.0 | 133 ± 8.1                   | 100 ± 46                          | 43.8                | OAP by diabetes nurses     |
| Matsuda    | Japan                           | 100         | 40.0    | Mean: 40.0             |            |                             | Mean: 7.0                         | 20.0                | OAP by a trained diabetes nurse |
| Partanen   | Finland                         | 112         | NS      | Mean: 10.9             | Range: 1.1–19.1 | 112/0                       | Mean: 4.6                        | 43.8                | OAP by two investigators    |
| Strauss    | Switzerland                     | 750         | 50.0    | Mean: 50.0             |            |                             | Mean: 10.9                        | 27.1                | OAP by physicians          |
| Pavlovic   | Czech Republic                  | 100         | 50.0    | Mean: 50.0             |            |                             | Mean: 10.9                        | 27.1                | OAP by diabetes nurses     |
| Berard     | Canada                          | 503         | 52.9    | Mean: 52.9             |            |                             | Median: 9.6                       | 54.0                | OAP by diabetes nurses     |
| Hajheydari | Iran                            | 220         | 56.0    | Mean: 56.0             |            |                             | Median: 9.6                       | 54.0                | OAP by diabetes nurses     |
| Ji        | China                           | 360         | 55.0    | Mean: 55.0             |            |                             | Median: 9.6                       | 54.0                | OAP by diabetes nurses     |
| Berard     | Canada                          | 215         | 52.2    | Mean: 52.2             |            |                             | Median: 9.6                       | 54.0                | OAP by diabetes nurses     |
| Hekman     | Canada                          | 220         | 50.0    | Mean: 50.0             |            |                             | Median: 9.6                       | 54.0                | OAP by diabetes nurses     |
| Sawatkar   | India                           | 220         | 50.0    | Mean: 50.0             |            |                             | Median: 9.6                       | 54.0                | OAP by diabetes nurses     |
| Youssef    | Egypt                           | 215         | 50.0    | Mean: 50.0             |            |                             | Median: 9.6                       | 54.0                | OAP by diabetes nurses     |
| Patil      | India                           | 220         | 50.0    | Mean: 50.0             |            |                             | Median: 9.6                       | 54.0                | OAP by diabetes nurses     |
| Ali        | Italy                           | 220         | 50.0    | Mean: 50.0             |            |                             | Median: 9.6                       | 54.0                | OAP by diabetes nurses     |
| Lin        | China                           | 220         | 50.0    | Mean: 50.0             |            |                             | Median: 9.6                       | 54.0                | OAP by diabetes nurses     |
| Hekman     | Canada                          | 220         | 50.0    | Mean: 50.0             |            |                             | Median: 9.6                       | 54.0                | OAP by diabetes nurses     |
| Youssef    | Egypt                           | 215         | 50.0    | Mean: 50.0             |            |                             | Median: 9.6                       | 54.0                | OAP by diabetes nurses     |
| Patil      | India                           | 220         | 50.0    | Mean: 50.0             |            |                             | Median: 9.6                       | 54.0                | OAP by diabetes nurses     |
| Ali        | Italy                           | 220         | 50.0    | Mean: 50.0             |            |                             | Median: 9.6                       | 54.0                | OAP by diabetes nurses     |
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| Hekman     | Canada                          | 220         | 50.0    | Mean: 50.0             |            |                             | Median: 9.6                       | 54.0                | OAP by diabetes nurses     |
| Youssef    | Egypt                           | 215         | 50.0    | Mean: 50.0             |            |                             | Median: 9.6                       | 54.0                | OAP by diabetes nurses     |
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| Ali        | Italy                           | 220         | 50.0    | Mean: 50.0             |            |                             | Median: 9.6                       | 54.0                | OAP by diabetes nurses     |
| Lin        | China                           | 220         | 50.0    | Mean: 50.0             |            |                             | Median: 9.6                       | 54.0                | OAP by diabetes nurses     |

[†] Seven European countries: Sweden, Belgium, Germany, France, Italy, Spain and the UK; [‡] 16 countries: USA, Russia, the Netherlands, Belgium, France, Spain, Italy, Switzerland, the UK and Ireland, Denmark, Sweden, Germany, China, Portugal, and Finland.
Quality assessment
We used a modified version of the Newcastle–Ottawa Scale to assess the methodological quality of every study included in the present meta-analysis. The total score ranges from 0 to 5, with ≥3 points indicating low risk of bias and <3 points indicating high risk of bias. The scale assesses quality in several domains: sample representativeness and size, comparability between respondents and non-respondents, ascertainment of LH, and statistical quality. The detailed assessment process can be seen in Appendix S2.

Statistical analysis
Data analysis was carried out using the meta-analysis software Stata version 12 (StataCorp, College Station, TX, USA). For evaluation of the pooled effect, a 95% confidence interval (CI) was considered, and statistical significance was set at a P < 0.05. We used random effects to pool studies reporting the prevalence of LH in patients with diabetes mellitus. Between-study heterogeneity was assessed by the I² with thresholds of ≥25%, ≥50% and ≥75% indicating low, moderate and high heterogeneity, respectively. The influence of an individual study on the overall prevalence estimate was explored by consecutively excluding each study in sensitivity analyses. Subgroup analyses were undertaken based on overall study quality, sample size, country of origin, type of diabetes mellitus and publication year, when there was more than one study in the subgroup. Funnel plots and Egger’s test were combined to explore the potential publication bias in this meta-analysis.

RESULTS
Characteristics of the participants in selected studies
The Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) statement was used to outline the selection process for eligible studies (Figure 1). The characteristics of the included studies are presented in Table 1. A total of 26 published studies matched the inclusion criteria, reporting on a total of 12,493 patients with diabetes mellitus. Interrater reliability of reviewers regarding study relevancy was high (Kappa = 0.86). Nine studies took place in Asia, 14 in Europe and one each in North America, Africa and a mix of different countries. The median of the mean ages was 46 years (range 6.5–63.8 years), and the median percentage of males represented in the sample was 50% (range 27.3–59.1%). In addition, the median number of participants per study was 228 (range 54–4352), the median of mean disease duration was 10.0 years (range 2.8–17.0 years) and the median of mean insulin treatment duration was 9.3 years (range 3.0–15.0 years). When evaluated by the modified Newcastle–Ottawa quality assessment criteria, out of 5 possible points, one study received 5 points, seven studies received 4 points, 14 received 3 points, 22, 24, 27, 30, 31, 33 received 2 points, and one received 1 point.

Sensitivity and subgroup analyses
Sensitivity analyses showed that the exclusion of studies with less sample representativeness (46%, 95% CI 36–55%), and fewer comparable respondents and non-respondents (39%, 95% CI 25%–53%) tended to increase the prevalence of LH. The sensitivity analyses through omitting studies one-by-one showed no abnormalities, and the result can be seen in Appendix S3. The subgroup analyses were carried out according to sample size, overall quality, publication year, country of origin and type of diabetes mellitus. Table 2 suggests LH prevalence estimates according to subgroup analysis. The results showed that studies with sample sizes <200 had higher LH estimates (40%, 95% CI 30–49% vs 37%, 95% CI 26–47%). When evaluated by Newcastle–Ottawa criteria, studies with lower total overall quality scores yielded higher LH estimates (43%, 95% CI 28–57% vs 37%, 95% CI 27–46%). In contrast with clinical interviews, more recent publications tended to yield higher LH prevalence estimates. The subgroup analyses for country of origin showed that LH prevalence among Asians tended to be higher than Europeans (41%, 95% CI 27–55% vs 37%, 95% CI 25–49%). The subgroup analyses for diabetes mellitus type showed that LH prevalence among patients with type 2 diabetes mellitus (49%, 95% CI 23–74%) tended to be higher than type 1 diabetes mellitus (34%, 95% CI 19–49%) and a mixed type of diabetes mellitus (37%, 95% CI 25–48%; Figure 2).

Table 2 | Impact of study characteristics on prevalence estimates for lipohypertrophy in diabetes mellitus patients: Subgroup analyses

| Subgroup analysis | n | 95% CI | I² (%) | P-value |
|-------------------|---|--------|--------|---------|
| Sample size       |   |        |        |         |
| <200              | 8 | 0.40 (0.30–0.49) | 89.7 | 0.000* |
| ≥200              | 18| 0.37 (0.26–0.47) | 99.4 | 0.000* |
| Overall quality   |   |        |        |         |
| <3 points (low quality) | 4 | 0.43 (0.28–0.57) | 92.8 | 0.000* |
| ≥3 points (high quality) | 22| 0.37 (0.27–0.46) | 99.2 | 0.000* |
| Publication year  |   |        |        |         |
| 1990s             | 3 | 0.34 (0.19–0.48) | 94.5 | 0.000* |
| 2000s             | 6 | 0.32 (0.16–0.49) | 98.9 | 0.000* |
| 2010–              | 17| 0.40 (0.32–0.48) | 98.5 | 0.000* |
| Country of origin |   |        |        |         |
| Europe            | 14| 0.37 (0.25–0.49) | 98.8 | 0.000* |
| Asia              | 9 | 0.41 (0.27–0.55) | 99.0 | 0.000* |
| Africa            | 1 | –      |        |         |
| North America     | 1 | –      |        |         |
| Mixed             | 1 | –      |        |         |
| DM type           |   |        |        |         |
| T1DM              | 10| 0.34 (0.19–0.49) | 98.6 | 0.000* |
| T2DM              | 3 | 0.49 (0.23–0.74) | 99.4 | 0.000* |
| T1DM and T2DM     | 10| 0.37 (0.25–0.48) | 98.3 | 0.000* |
| NS                | 3 | 0.41 (0.29–0.54) | 96.6 | 0.000* |

*P < 0.001. I² ≥25% (low), ≥50% (moderate), ≥75% (high). CI, confidence interval; DM, diabetes mellitus; LH, lipohypertrophy; NS, not stated; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.
Assessment of publication bias
Assessment of publication bias showed no publication bias, according to the Egger’s test (Egger: bias = 2.35, 95% CI – 5.93–10.62, P = 0.56) and the funnel plot (Figure 3).

DISCUSSION
The present systematic review and meta-analysis of 26 studies involved 12,493 patients with diabetes mellitus. Different studies had roughly the same definition of LH, namely, visible and
palpable fatty swellings of subcutaneous adipose tissue at insulin injection or infusion sites. The gold standard for detecting of LH is skin ultrasound scans. The value of ultrasound examination can be seen in the case of a study carried out by Volkova et al., which showed that just eight of 50 participants had clinically evident LH, but 33 of the remaining showed ultrasound evidence of LH.

However, instead of detecting LH using ultrasound examination, most studies detected LH by observing and palpating the injection sites of patients using insulin. Up to now, there is no unified method of visual inspection and palpation. Just three of the included studies described the methods further, and the methods referred to by Ji et al. are more preferable. They took into consideration the body positions of patients when they evaluated the injection sites. For abdominal examinations, patients lay supine; for the thigh, they sat with knees bent and feet on the floor; for buttocsk, patients stood; and for arms, patients could sit or stand. The concrete method was that examiners washed their hands and kept them warm, and for examiners, patients could sit or stand. The concrete method was that examiners washed their hands and kept them warm, then they daubed ultrasound gel on their hands and the injection sites, and the patients were then examined in a specific position by trained staff in a warm environment to avoid shivering, with oblique lighting to assist visual inspection. Light-to-moderate pressure with small sweeps of the fingertips was used to detect LH.

The reason why the researchers prefer observation and palpation is that it is expensive and time-consuming to investigate LH by ultrasound scans just for the purpose of screening. In addition, carrying out biopsies for histopathological examination to detect LH is a reliable method, and it can avoid the misdiagnosis of amyloid lumps as LH, because they are hard to distinguish from each other by physical examination, but it is not practical or economical. Sandro et al. reported a suitable palpation technique to identify LH, which reached a 97% consistency rate as compared with the gold standard. Future studies can take advantage of this approach to detect LH in a cost-effective way. At present, patients are not competent to identify LH by themselves, so we discarded studies involving this condition unless the samples were large. Furthermore, not all studies mentioned that trained medical professionals were responsible for the detection of LH, which gave implications for future studies, as non-professionals are likely to overestimate or underestimate the prevalence of LH. We found that the prevalence of LH ranged from 1.9% to 73.4%, and the overall prevalence was 38% (95% CI 29–46%).

Subgroup analysis revealed some interesting findings. The present study found that the prevalence of LH among Asians tended to be higher than among Europeans. This inconsistency might have something to do with social and cultural elements. However, we also found that most studies carried out in Asia were published later, which was in line with the outcome that recent publications were associated with increased LH prevalence among diabetes mellitus patients. In addition, the result of subgroup analysis by type of diabetes mellitus showed that patients with type 2 diabetes mellitus were more likely to develop LH than patients with type 1 diabetes mellitus. Among patients with type 2 diabetes mellitus, some of them showed that participants with type 1 diabetes mellitus developed LH more easily, though other studies failed to come to such a conclusion. This discrepancy might be due to the number of patients with different types of diabetes mellitus in those articles being unbalanced. Typically, one study had a total sample of 401 participants, but there were just 26 patients living with type 1 diabetes mellitus, the rest of the sample were all patients with type 2 diabetes mellitus. Although studies varied widely in terms of quality, our sensitivity analyses suggested that LH prevalence estimates were reasonably stable. Furthermore, studies with lower total overall quality scores yielded higher LH estimates. The present study also showed that studies with sample size <200 had higher LH estimates.

Because LH is associated with erratic glucose control, increased risk of chronic complications, and increased economic burden, these findings stressed that it is vital that diabetes nurses recognize this condition by inspecting and palpating insulin injecting sites regularly, and draw up a plan for patients to avoid the development of LH. Not only does LH have an influence on disease management, but it can also affect the appearance of a person. Furthermore, there is no established therapeutic method for LH, and people with severe LH must have these parts of the body removed by surgery, therefore it is important that we discover these sites early so as to let them disappear slowly when the degree of LH is not that serious.

The present review had several limitations. First, the heterogeneity of both total population and subgroup was high, part of which could not be explained. Unexamined factors, such as age, sex, diabetes mellitus duration, insulin treatment duration and methods for detecting of LH might also contribute to the risk for LH, but we could not analyze these factors because of incomplete data. Second, the studies searched were restricted to articles published in English. Third, most studies did not use...
gold standard for detecting of LH, so there might be significant interobserver variation in the reporting of this condition.

**DISCLOSURE**
The authors declare no conflict of interest.

**REFERENCES**

1. International Diabetes Federation. IDF diabetes atlas. 7th ed. http://www.diabetesatlas.org/. [accessed August 21, 2016].

2. Cunningham MT, Mckenna M. Lipohypertrophy in insulin-treated diabetes: Prevalence and associated risk factors. *J Diabetes Investig* Vol. 9 No. 3 May 2018

3. Blanco M, Hernández MT, Strauss KW, et al. Prevalence and risk factors of lipohypertrophy in insulin-injecting patients with diabetes. *Diabetes Metab* 2013; 39: 445–453.

4. Smith KJ, Rabasa-Lhoret R, Strychar I, et al. Frequency of lipohypertrophy and lipodystrophy induced by recombinant human insulin. *Diabetes Metab* 2017; 43: 1050–1058.

5. Noor S, Khan RU, Ahmad J. Understanding diabetic foot infection and its management. *Diabetes Metab Syndr* 2017; 11: 149–156.

6. Mowatt L. Diabetic retinopathy and its risk factors at the University Hospital in Jamaica. *Middle East Afr J Ophthalmol* 2013; 20: 321–326.

7. Boer IHD, Group FE. Kidney disease and related findings in diabetes treated diabetes: Prevalence and associated risk factors. *Diabetes Technol Ther* 2017; 19: 236–239.

8. Noor S, Khan RU, Ahmad J. Understanding diabetic foot infection and its management. *Diabetes Metab Syndr* 2017; 11: 149–156.

9. Ji L, Sun Z, Li Q, et al. Lipohypertrophy in China: prevalence, risk factors, insulin consumption, and clinical impact. *Diabetes Technol Ther* 2017; 19: 61–67.

10. Pavlovic MD, Milenkovic T, Dinic M, et al. The prevalence of cutaneous manifestations in young patients with Type 1 diabetes. *Diabetes Care* 2014; 37: 24–30.

11. Li FF, Fu SM, Liu ZP, et al. Injection sites lipohypertrophy among 736 patients with type 2 diabetes of different-grade hospitals. *Int J Clin Exp Med* 2016; 9: 13178–13183.

12. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol* 2010; 25: 603–605.

13. Panin N, Leoncini E, Belvis GD, et al. Evaluation of the endorsement of the preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement on the quality of published systematic review and meta-analyses. *PLoS ONE* 2013; 8: e683138.

14. Al Hayek AA, Robert AA, Braham RB, et al. Frequency of lipohypertrophy and associated risk factors in young patients with Type 1 diabetes: a cross-sectional study. *Diabetes Ther* 2016; 7: 259–267.

15. Al Ajlouni M, Abu-Jbara M, Batieha A, et al. Prevalence of lipohypertrophy and associated risk factors in insulin-treated patients with type 2 diabetes mellitus. *Int J Endocrinol Metab* 2015; 13: e20776.

16. Vardar B, Kizilca S. Incidence of lipohypertrophy in diabetic patients and a study of influencing factors. *Diabetes Res Clin Pract* 2007; 77: 231–236.

17. Hajheydari Z, Kashi Z, Akha Q, et al. Frequency of lipohypertrophy induced by recombinant human insulin. *J Diabetes Investig* Vol. 9 No. 3 May 2018

18. Sawatkar GU, Kanwar AJ, Dogra S, et al. Spectrum of cutaneous manifestations of type 1 diabetes mellitus in 500 South Asian patients. *Br J Dermatol* 2014; 171: 1402–1406.

19. Ji J, Lou Q. Insulin pen injection technique survey in patients with type 2 diabetes in mainland China in 2010. *Curr Med Res Opin* 2014; 30: 1087–1093.

20. Patil M, Sahoo J, Kamalanathan S, et al. Assessment of insulin injection techniques among diabetes patients in a tertiary care centre. *Diabetes Metab Syndr* 2016. https://doi.org/10.1016/j.dsx.2016.09.010

21. Hernar I, Haltbakk J, Broström A. Differences in depression, treatment satisfaction and injection behaviour in adults with type 1 diabetes and different degrees of lipohypertrophy. *J Clin Nurs* 2017. https://doi.org/10.1111/jocn.13801

22. Hauner H, Stockamp B, Haastert B. Prevalence of lipohypertrophy in insulin-treated diabetic patients and predisposing factors. *J Clin Nurs* 1996; 104: 106–110.

23. Ibarrac SD, Bsc FG. Factors related to lipohypertrophy and lipoatrophy complicating treatment with highly purified bovine and porcine insulins. *Postgrad Med J* 1988; 64: 850–853.

24. Partanen TM, Rissanen A. Insulin injection practices. *Practical Diabetes Int* 2000; 17: 252–254.

25. Raile K, Noelle V, Landgraf R, et al. Insulin antibodies are associated with lipoatrophy but also with lipohypertrophy in children and adolescents with type 1 diabetes. *Exp Clin Endocrinol Diabetes* 2001; 109: 393–396.

26. Kenneth Strauss MD, Gols HD, Hannet I, et al. Pan-European epidemiologic study of insulin injection technique in patients with diabetes. *Practical Diabetes* 2002; 19: 71–76.

27. Schober E, Ramı B. Dermatological side effects and complications of continuous subcutaneous insulin infusion in preschool-age and school-age children. *Pediatr Diabetes* 2009; 10: 198–201.

28. Grassi G, Scuntero P, Trepiccioni R, et al. Optimizing insulin injection technique and its effect on blood glucose control. *J Clin Transl Endocrinol* 2014; 1: 145–150.

29. Van Munster HE, Van PM, Voorhoeve PG, et al. Dermatological complications of insulin therapy in children with type 1 diabetes. *Eur Diabetes Nurs* 2015; 11: 79–84.

30. Binder E, Lange O, Edlinger M, et al. Frequency of dermatological side effects of continuous subcutaneous insulin infusion in children and adolescents with type 1 diabetes. *Exp Clin Endocrinol Diabetes* 2015; 123: 260–264.
31. Berard L, Cameron B. Injection technique practices in a population of Canadians with diabetes: results from a recent patient/diabetes educator survey. Can J Diabetes 2015; 39: 146–151.

32. Youssef RM, Ibrahim A, Amin IM, et al. Cutaneous manifestations among Egyptian children and adolescents with type 1 diabetes. Egypt Pediatr Assoc Gaz 2016; 64: 44–49.

33. De Coninck C, Frid A, Gaspar R, et al. Results and analysis of the 2008–2009 insulin injection technique questionnaire survey. J Diabetes 2010; 2: 168–179.

34. Gentile S, Guarino G, Giancaterini A, et al. A suitable palpation technique allows to identify skin lipohypertrophic lesions in insulin-treated people with diabetes. SpringerPlus 2016; 5: 563.

35. Volkova NYI, Davidenko IYYE. Lipohypertrophy in patients receiving insulin therapy: state of the art. Diabetes Mellitus. Saharnyj Diabet 2011; 14: 86–89.

36. Nilsson MR. Insulin amyloid at injection sites of patients with diabetes. Amyloid 2016; 23: 139–147.

37. Brun A, Comparin JP, Vouillaume D, et al. Insulin-induced lipohypertrophy treated by liposuction. Ann Chir Plast Esthet 2007; 52: 218–221.

SUPPORTING INFORMATION
Additional Supporting Information may be found in the online version of this article:

Appendix S1 | The detailed search strategy.
Appendix S2 | Quality assessment.
Appendix S3 | Sensitivity analyses through consecutively excluding each study.