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REVIEW ARTICLE

Relationship Between Lipohypertrophy, Glycemic Control, and Insulin Dosing: A Systematic Meta-Analysis

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Abstract

Background: Lipohypertrophy is a common complication in patients with diabetes receiving insulin therapy. There is a lack of consensus regarding how much lipohypertrophy affects diabetes management. Our study aimed to assess the potential correlation between lipohypertrophy and glycemic control, as well as insulin dosing in patients with diabetes.

Methods: We performed a systematic review followed by a meta-analysis to collect data about glycemic control and insulin dosing in diabetic patients with and without lipohypertrophy. To identify relevant studies published in English, we searched medical databases (MEDLINE/PubMed, Embase, and CENTRAL) from 1990 to January 20, 2023. An additional hand-search of references was performed to retrieve publications not indexed in medical databases. Results of meta-analyses were presented either as prevalence odds ratios (pORs) or mean differences (MDs) with 95% confidence intervals (95% CIs). This study was registered on PROSPERO (CRD42023393103).

Results: Of the 5540 records and 240 full-text articles screened, 37 studies fulfilled the prespecified inclusion criteria. Performed meta-analyses showed that patients with lipohypertrophy compared with those without lipohypertrophy were more likely to experience unexplained hypoglycemia (pOR [95% CI] = 6.98 [3.30–14.77]), overall hypoglycemia (pOR [95% CI] = 6.65 [1.37–32.36]), and glycemic variability (pOR [95%

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CI] = 5.24 [2.68–10.23]). Patients with lipohypertrophy also had higher HbA1c (MD [95% CI] = 0.55 [0.23–0.87] %), and increased daily insulin consumption (MD [95% CI] = 7.68 IU [5.31–10.06]).

Conclusions: These results suggest that overall glycemic control is worse in patients with lipohypertrophy than in those without this condition.

Introduction

LIPOHYPERTROPHY IS A common complication in patients with diabetes treated with insulin therapy.[1] Several risk factors for developing lipohypertrophy among insulin-injecting patients have been considered, including lack of systemic rotation,[2–4] needle reuse,[2,4,5] needle length,[3,6,7] and number of daily injections.[8] The condition is primarily characterized by the enlargement of adipocytes that manifests by nodular swelling and the induration of fat tissue around the injection sites.[9]

In clinical practice, lipohypertrophy is usually diagnosed by physical examination, that is, visually and by palpation, and the most common presentation of lipohypertrophic nodules are those of large visible and esthetically displeasing mounds. However, increasing evidence suggests lipohypertrophic nodules exist in various forms, many of which are not easily visible or detectable by palpation.[10]

As physical examination methods vary between countries, as evident in the lack of uniformity in the approaches to visual and palpation examination methods, new methods of lipohypertrophy detection have emerged, including ultrasonographic skin scanning.[11,12] A recent meta-analysis, based on data from 26,865 patients, showed that lipohypertrophy is a common health problem with a worldwide prevalence of 41.8% (95% CI: 35.9%–47.6%) among patients with diabetes.[13] However, when considering studies that specifically utilized ultrasound sonography, these figures can rise as high as 86.5%, suggesting an underappreciated prevalence of this complication.[14,15]

Published studies suggest that many insulin-treated patients have significant deficiencies in their injection technique. They often fail to ensure proper site rotation and show a preference for injecting insulin into lipohypertrophic nodules, as these areas are less sensitive to pain.[11] Available data indicate that insulin injections into lipohypertrophic areas may occur in up to 95.3% of patients with diabetes receiving insulin therapy.[16–18]

Lack of thorough understanding of the possible consequences of lipohypertrophy may have an unaware impact on the efficacy of antihyperglycemic therapy in individual patients. Driven by the high number of people living with diabetes and the high prevalence of lipohypertrophy, this represents an unnoticed global health problem.

Aside from the apparent esthetic influence on patients' well-being and self-image, pharmacological studies suggest that different structural properties of lipohypertrophic lesions may affect insulin absorption and metabolism.[19,20] The insulin release from lipohypertrophic tissue is considered slower and more unpredictable than from normal fat tissue, which may result in excessive insulin dosing to achieve a pharmacological effect.[9] However, available clinical evidence regarding the possible relationship between the presence of lipohypertrophy and glycemic control is contradictory.

Previous studies reported an increased risk of uncontrolled glycemia, glycemic variability, and episodes of unexplained hypoglycemia in patients with lipohypertrophy.[2,4,6] For example, Gentile et al. found that 46.2% of patients with lipohypertrophy experienced one or more episodes of hypoglycemia compared with 6.8% of patients without lipohypertrophy.[16] In contrast, other studies found no such association.[21–23] According to Kamrul-Hasan et al., the prevalence of hypoglycemia was comparable among patients with and without lipohypertrophy.[18] Hence, clarifying the possible link between the presence of lipohypertrophy and glycemic control is needed.

Our research aimed to critically evaluate and explain the potential relationship between lipohypertrophy and outcomes related to glycemic control (e.g., hypoglycemia events, HbA1c, and glycemic variability) and insulin dosing. We performed a systematic literature review followed by a meta-analysis to synthesize the current knowledge of this important clinical issue. We hope our results will provide clinicians with additional evidence-based information for the best management of diabetic patients and help identify critical knowledge gaps and further directions for research in this area.

Materials and Methods

Search strategy and selection criteria

This systematic review with a meta-analysis followed the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) 2020 guidelines.[24] We searched for studies reporting glycemic control (HbA1c, glycemic variability, uncontrolled glycemia, or continuous glycemia monitoring data), episodes of hypoglycemia (symptomatic, asymptomatic, severe, unexplained, and overall), hyperglycemia, and daily insulin doses in diabetic patients with lipohypertrophy (LH+) and without lipohypertrophy (LH−) who were treated with subcutaneous antihyperglycemic therapy administered by pens or syringes.

As therapy with glucagon-like peptide-1 (GLP-1) receptor agonists has become more prevalent in recent years, we also sought to retrieve data for the group using these antidiabetic agents in addition to insulin-treated patients. We defined glycemic variability as blood glucose oscillations <60 to >250 mg/dL at least three times a week or more than two unexplained glycemic fluctuations per week. Unexplained hypoglycemia was determined as hypoglycemic episodes without a definable precipitating event, such as a change in medication, diet, or activity. Uncontrolled glycemia included the proportion of patients with HbA1c >7.0%.

We included randomized, observational, and cross-sectional studies published in English since 1990. We justified the publication date limitation because the standard of diabetes care and insulin therapy had changed in the past decades, which could have influenced the meta-analysis

results. Studies were excluded if they were conducted in patients administering insulin by nonautomated pumps or other sensor-augmented devices for continuous subcutaneous infusion. Other exclusion criteria included studies describing patients treated mainly (≥80%) with animal insulins, studies published only as conference proceedings, and studies with data presentations unsuitable for cumulation.

The systematic search was performed in MEDLINE (through PubMed), Embase, and CENTRAL (through The Cochrane Library) databases on January 20, 2023, using the keywords ''diabetes'' and ''lipohypertrophy.'' Detailed search strategies are provided in the Supplementary Appendix SA1 (Supplementary Tables S1–S3). A hand-search of references of the included studies was performed to retrieve other relevant publications not indexed in searched medical databases.

If the same research group published more than one study, we contacted the corresponding authors to ensure that studies published by the same authors do not duplicate data for the same patients. Two independent reviewers (A.S.-T. and M.M.) selected the studies according to the protocol and predefined eligibility criteria (Table 1). Any disagreements between reviewers on the full-text stage selection process were resolved by consensus.

Data analysis

Two reviewers (A.S.-T. and M.M.) performed data extraction independently. All discrepancies between reviewers were discussed and resolved. Extracted items included the design of studies, baseline population characteristics, details of antihyperglycemic therapy, analyzed outcomes (HbA1c, glycemic variability, uncontrolled glycemia, continuous glucose monitoring data, hypo/hyperglycemia, and daily insulin doses), and their definitions. The risk of bias was assessed using Joanna Briggs Institute (JBI) tools for cross-sectional[25] and quasi-experimental[26] studies.

We conducted meta-analyses comparing data for LH+ and LH− only if two or more studies reported the same outcome. Results of meta-analyses were presented either as prevalence odds ratios (pORs) for the proportion of patients with an event or as mean differences (MDs) for outcomes expressed by means and standard deviations. All results were given with 95% confidence intervals (95% CIs). We used a random model (DerSimonian and Laird) for data cumulation if significant between-study heterogeneity was observed (P-value for Cochrane Q test <0.10 and $I^2 > 50\%$). In other cases, a fixed model was chosen. If available, we also extracted P-values for comparisons reported by authors of the individual studies.

We performed subgroup analyses to explore the effect of diabetes mellitus type, geographic region, duration of insulin therapy, and a type of lipohypertrophy measurement on meta-analyses results. We also conducted sensitivity analyses, including only studies published in the past 10 years, to determine if the publication date impacted meta-analyses results. Subgroup and sensitivity analyses were performed only for outcomes, including at least 10 studies in the primary meta-analyses. The risk of publication bias for meta-analysis of at least 10 studies was assessed by Eggers plots. For all statistical analyses, Sophie ver. 1.5.0 software was used (validated with STATA ver. 10.0).

The study was registered on the PROSPERO database (CRD42023393103).

Results

Of the 5540 records identified during databases and references search, 240 full-text articles were assessed for eligibility, of which 200 were excluded. Finally, 37 studies described in 40 articles were included in the systematic meta-analysis (Table 2 and Supplementary Fig. S1). All excluded studies with reasons are provided in the Supplementary Appendix SA1 (Supplementary Table S4).

Most of the included studies were cross-sectional (35 studies) and single-center (24 studies). Only two studies[17,55] were prospective and quasi-experimental. Five studies included only individuals with type 1 diabetes (T1DM), 11 with type 2 diabetes (T2DM), patients with either type of diabetes participated in 20 studies, and 1 study did not report information about diabetes type.[46] Three studies[2,21,47] focused on the pediatric population.

TABLE 1. INCLUSION AND EXCLUSION CRITERIA

PICO	Inclusion criteria	Exclusion criteria
Population	Patients with diabetes treated with insulin or GLP-1 analogs administered by pens or syringes	Participants using insulin pumps exclusively Most of the participants (≥80%) used insulins other than humans and analogs
Intervention (exposure)	Presence of lipohypertrophy (lipodystrophy)	Not applicable
Comparator (control)	Lack of lipohypertrophy (lipodystrophy)	Not applicable
Outcomes	Glycemic control (glycemic variability, HbA1c, and CGM data), episodes of hypoglycemia and hyperglycemia (symptomatic, asymptomatic, severe, and unexplained), and daily insulin dosage	Other than defined Data presentation unsuitable for cumulation (e.g., continuous endpoints presented as medians)
Study type	Randomized clinical trials and observational studies (cohort, case–control, and cross-sectional) published in English	Studies published only as conference abstracts or posters Studies published before 1990 Studies published in languages other than English

CGM, Continuous glucose monitoring; GLP-1, glucagon-like peptide-1.

TABLE 2. SUMMARY OF THE INCLUDED STUDIES

Study	Study design (location)	Number of patients (LH+/LH−)	LH measurement	Diabetes type	Population	Duration of diabetes	Duration of insulin therapy
Abujbara et al.[7]	Cross-sectional, single-center (Jordan)	851 (477/374)	Visual inspection and palpation	T1DM, T2DM	Unknown	12.3 (8.1)	7.0 (6.2)
Al Ajlouni et al.[28]	Cross-sectional, single-center (Jordan)	1090 (407/683)	Visual inspection and palpation	Only T2DM	Only adults	13.5 (9–20)[a]	4.6 (5.0)
Al Hayek et al.[2]	Cross-sectional, single-center (Saudi Arabia)	174 (83/91)	Visual inspection and palpation	Only T1DM	Only children	6.1 (4.5)	Unknown
AlJaber et al.[29]	Cross-sectional, multicenter (Saudi-Arabia)	202 (80/122)	Visual inspection and palpation	Only T2DM	Only adults	16.9 (8.5)	8.5 (5.8)
Arora et al.[30]	Cross-sectional, single-center (India)	500 (290/210)	Visual inspection and palpation, USG in all patients	T1DM, T2DM	Unknown	Unknown	3.0 (2.5–5.0)[a]
Barola et al.[3]	Cross-sectional, single-center (India)	372 (231/141)	Visual inspection and palpation	Only T1DM	Children, adults	5.6 (5.3)	Unknown
Baruah et al.[5]	Cross-sectional, single-center (India)	748 (94/654)	Visual inspection and palpation	Only T2DM	Children, adults	12.2 (7.6)	3.4 (4.2)
Blanco et al.[4]	Cross-sectional, multicenter (Spain)	430 (277/153)	Visual inspection and palpation, USG in some patients	T1DM, T2DM	Children, adults	NA (6–15)[b]	NA (1–5)[b]
Bochanen et al.[17]	Prospective, quasi-experimental, multicenter (Belgium)	146 (92/54)	Visual inspection and palpation	T1DM, T2DM	Only adults	Unknown	Unknown
Cunningham and McKenna[31]	Cross-sectional, multicenter (Ireland)	55 (28/27)	Visual inspection and palpation	T1DM, T2DM	Unknown	Unknown	15.0 (12.6)
Frid et al.[32–34]	Cross-sectional, multicenter (Worldwide)	13,289 (3855/9344)	Visual inspection and palpation	T1DM, T2DM	Children, adults	13.2 (9.7)	8.7 (8.9)
Gentile et al.[35]	Cross-sectional, multicenter (Italy)	296 (169/127)	Visual inspection and palpation	T1DM, T2DM	Only adults	7.0 (2.0)	3.0 (1.0)
Gentile et al.[36]	Cross-sectional, multicenter (Italy)	1227 (718/509)	Visual inspection and palpation, USG in all patients	Only T2DM	Only adults	10.6 (7.9)	7.6 (6.0)
Gentile et al.[6]	Cross-sectional, multicenter (Italy)	780 (360/420)	Visual inspection and palpation, USG in all patients	T1DM, T2DM	Only adults	18.0 (11.0)	10.1 (2.1)
Gentile et al.[16]	Prospective, quasi-experimental, multicenter (Italy)	1160 (487/673)	Visual inspection and palpation, USG in some patients	Only T2DM	Only adults	15.8 (7.6)	7.6 (2.2)
Gunhan et al.[37]	Cross-sectional, single-center (Turkey)	345 (98/247)	Visual inspection and palpation	Only T2DM	Only adults	37.0 (8.5)	8.9 (5.7)
Gupta et al.[38]	Cross-sectional, single-center (India)	139 (97/42)	Visual inspection and palpation	Only T2DM	Only adults	8.7 (7.5)	Unknown
Hajheydari et al.[39]	Cross-sectional, single-center (Iran)	230 (35/185)	Visual inspection and palpation	T1DM, T2DM	Unknown	14.0 (8.5)	5.4 (6.0)
Hauner et al.[40]	Cross-sectional, single-center (Germany)	279 (66/213)	Visual inspection and palpation	T1DM, T2DM	Unknown	14.1 (9.5)	Unknown

(continued)

TABLE 2. (CONTINUED)

Study	Study design (location)	Number of patients (LH⁺/LH⁻)	LH measurement	Diabetes type	Population	Duration of diabetes	Duration of insulin therapy
Ji and Lou[41]	Cross-sectional, multicenter (China)	380 (134/246)	Visual inspection and palpation	Only T2DM	Only adults	Unknown	3.6 (4.1)
Ji et al.[23,42]	Cross-sectional, multicenter (China)	401 (213/188)	Visual inspection and palpation	T1DM, T2DM	Only adults	11.8 (7.3)	5.8 (4.5)
Kamrul-Hasan et al.[18]	Cross-sectional, multicenter (China)	847 (78/769)	Unknown	T1DM, T2DM	Unknown	9.8 (7.0)	3.8 (4.1)
Korkmaz et al.[43]	Cross-sectional, single-center (Turkey)	136 (119/17)	Only USG	T1DM, T2DM	Only adults	15.8 (9.2)	11.4 (8.3)
Kumar et al.[44]	Cross-sectional, single-center (India)	88 (60/28)	Visual inspection and palpation, USG in all patients	T1DM, T2DM	Only adults	26.4 (5.1)	6.5 (6.6)
Lin et al.[8]	Cross-sectional, single-center (China)	120 (83/37)	Visual inspection and palpation, USG in all patients	Only T2DM	Only adults	Unknown	6.6 (4.3)
Luo et al.[45]	Cross-sectional, single-center (China)	316 (270/46)	Visual inspection and palpation, USG in some patients	T1DM, T2DM	Only adults	12.8 (16.6–19.2)[a]	6.2 (2.9–10.4)[a]
Nawaz et al.[46]	Cross-sectional, single-center (Pakistan)	363 (83/280)	Unknown	Unknown	Children, adults	7.9 (4.5)	6.5 (3.7)
Omar et al.[47]	Cross-sectional, single-center (Egypt)	119 (62/51)	Visual inspection and palpation	Only T1DM	Only children	Unknown	Unknown
Pahuja et al.[48]	Cross-sectional, single-center (India)	96 (65/31)	Visual inspection and palpation	Only T2DM	Only adults	19.8 (NA)	6.8 (NA)
Pozzuoli et al.[22]	Cross-sectional, single-center (Italy)	352 (151/201)	Visual inspection and palpation	T1DM, T2DM	Unknown	20.4 (9.9)	9.1 (8.6)
Saeed et al.[49]	Cross-sectional, single-center (Pakistan)	360 (157/203)	Visual inspection and palpation	T1DM, T2DM	Unknown	14.7 (7.6)	8.5 (6.1)
Saez de Ibarra and Gallego[50]	Cross-sectional, single-center (Spain)	150 (78/72)	Visual inspection and palpation	T1DM, T2DM	Unknown	13.0 (9.0)	11.4 (7.9)
Singha et al.[51]	Cross-sectional, single-center (India)	95 (46/45)	Visual inspection and palpation, USG in all patients	Only T1DM	Unknown	Unknown	Unknown
Strollo et al.[52]	Cross-sectional, multicenter (Italy)	387 (298/98)	Visual inspection and palpation	T1DM, T2DM	Only adults	13.0 (9.0)	10.0 (9.0)
Arda Sürücü and OKurArslan[53]	Cross-sectional, single-center (Turkey)	436 (191/245)	Visual inspection and palpation	Only T2DM	Only adults	Unknown	Unknown
Thewjitcharoen et al.[54]	Cross-sectional, single-center (Thailand)	400 (149/251)	Visual inspection and palpation, USG in all patients	T1DM, T2DM	Unknown	23.0 (10.2)	11.4 (8.7)
Tsadik et al.[21]	Cross-sectional, single-center (Ethiopia)	176 (103/73)	Visual inspection and palpation	Only T1DM	Only children	Unknown	Unknown

Continuous data are given as mean (SD) unless otherwise stated.
[a]Median (IQR).
[b]Median (range).
IQR, interquartile range; LH, lipohypertrophy; NA, not available; SD, standard deviation; T1DM, type 1 diabetes; T2DM, type 2 diabetes; USG, ultrasonography.
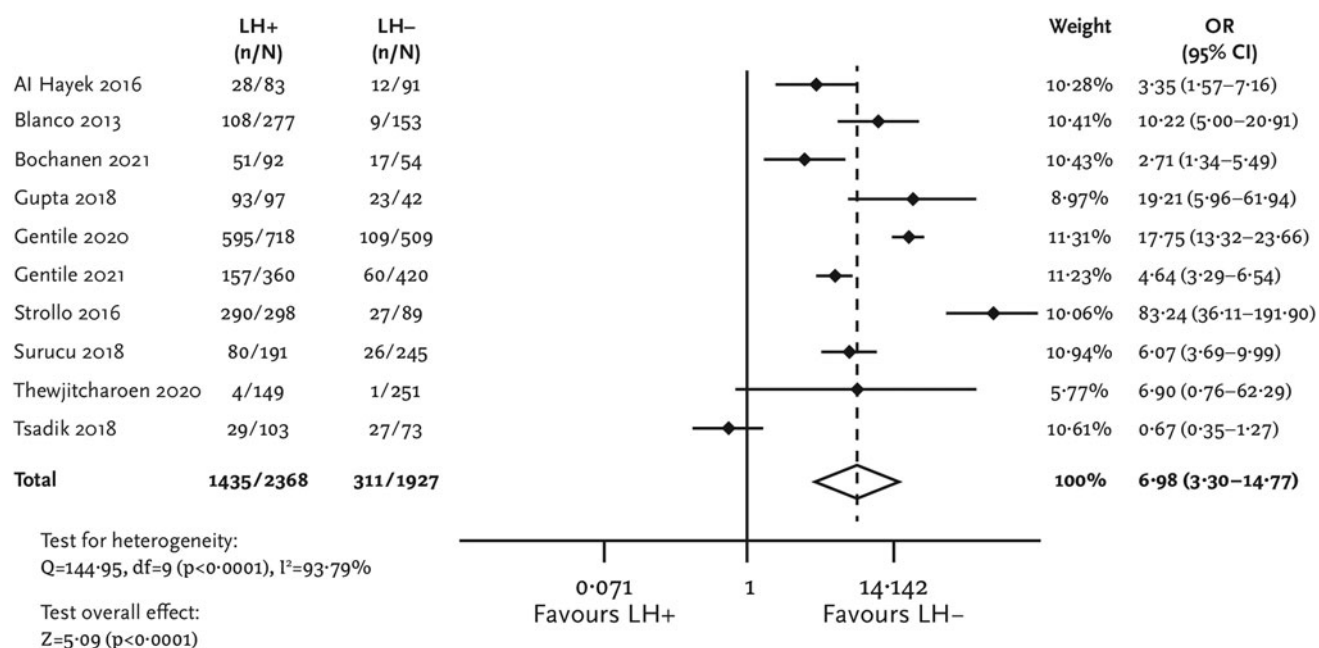
	LH+ (n/N)	LH– (n/N)		Weight	OR (95% CI)
Al Hayek 2016	28/83	12/91		10·28%	3·35 (1·57–7·16)
Blanco 2013	108/277	9/153		10·41%	10·22 (5·00–20·91)
Bochanen 2021	51/92	17/54		10·43%	2·71 (1·34–5·49)
Gupta 2018	93/97	23/42		8·97%	19·21 (5·96–61·94)
Gentile 2020	595/718	109/509		11·31%	17·75 (13·32–23·66)
Gentile 2021	157/360	60/420		11·23%	4·64 (3·29–6·54)
Strollo 2016	290/298	27/89		10·06%	83·24 (36·11–191·90)
Surucu 2018	80/191	26/245		10·94%	6·07 (3·69–9·99)
Thewjitcharoen 2020	4/149	1/251		5·77%	6·90 (0·76–62·29)
Tsadik 2018	29/103	27/73		10·61%	0·67 (0·35–1·27)
Total	**1435/2368**	**311/1927**		**100%**	**6·98 (3·30–14·77)**

Test for heterogeneity:
Q=144·95, df=9 (p<0·0001), I²=93·79%

Test overall effect:
Z=5·09 (p<0·0001)

0·071 Favours LH+   1   14·142 Favours LH–

FIG. 1. Forest plot for unexplained hypoglycemia.

The size of the population in the included studies varied from 55[31] to 13,289[9] participants. The quality of the research was diverse based on JBI scales (4–8/8 points for cross-sectional studies and 5–6/9 points for quasi-experimental), although no study was excluded from meta-analyses due to the high risk of bias. Detailed characteristics of the included studies are presented in the Supplementary Appendix SA1 (Supplementary Tables S5–S17).

The primary analysis showed that patients with lipohypertrophy were more likely to experience unexplained hypoglycemia (pOR [95% CI] = 6.98 [3.30–14.77]; Fig. 1) and overall hypoglycemia (pOR [95% CI] = 6.65 [1.37–32.36]; Fig. 2) compared with patients without lipohypertrophy. No between-group difference was found regarding symptomatic and severe hypoglycemia. Data for other endpoints related to hypoglycemia were presented only in individual studies, and performing meta-analyses for these outcomes was impossible.

Patients with lipohypertrophy also had significantly higher values of HbA1c than those without lipohypertrophy (MD [95% CI] = 0.55 [0.23–0.87] %; Fig. 3). Uncontrolled glycemia, defined as HbA1c values >7%, was also more com-mon among the lipohypertrophy group (pOR [95% CI] = 2.77 [1.62–4.73]; Fig. 4).

The presence of lipohypertrophy was also associated with a higher prevalence of glycemic variability among patients with diabetes (pOR [95% CI] = 5.24 [2.68–10.23]; Fig. 5). Mean values of glycemic variability based on only two studies[35,36] were higher in the lipohypertrophy group com-pared with the no lipohypertrophy group (MD [95% CI] = 100.20 [93.70–106.69] mg/dL).

Patients with lipohypertrophy were treated with higher insulin doses compared with those without lipohypertrophy (MD [95% CI] = 7.68 IU [5.31–10.06]; Fig. 6). The differ-ence remained significant even if insulin doses were adjusted to the individuals' body weight (MD [95% CI] = 0.06 [0.01–0.12] IU/kg). Only a few identified studies reported data for hyperglycemia and continuous glucose monitoring. Results for these endpoints are given in the Supplementary Appendix SA1 (Supplementary Tables S35 and S36).

Performed sensitivity analyses indicate that the publica-tion date did not significantly impact meta-analysis results for primary outcomes, including unexplained hypoglycemia,

	LH+ (n/N)	LH– (n/N)		Weight	OR (95% CI)
Gentile 2022	289/487	46/673		33·75%	19·89 (14·02–28·23)
Kamrul-Hasan 2020	36/78	275/769		33·31%	1·54 (0·96–2·46)
Nawaz 2023	58/83	55/280		32·93%	9·49 (5·45–16·51)
Total	**383/648**	**376/1722**		**100%**	**6·65 (1·37–32·36)**

Test for heterogeneity:
Q=73·82, df=2 (p<0·0001), I²=97·29%

Test overall effect:
Z=2·35 (p<0·0190)

0·071 Favours LH+   1   14·142 Favours LH–
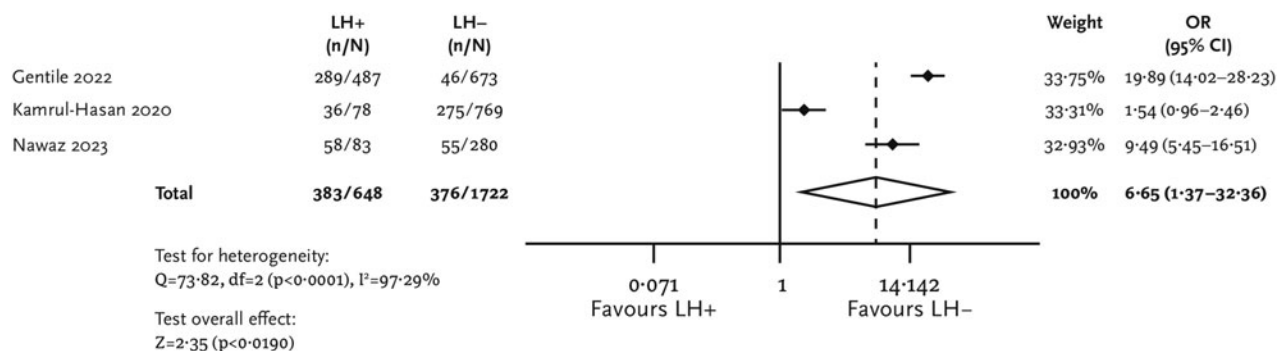
FIG. 2. Forest plot for overall hypoglycemia.

	LH+			LH−			Weight	WMD (95% CI)
	N	Mean	SD	N	Mean	SD		
Al Jaber 2020	80	9·53	1·60	122	9·14	1·70	4·13%	0·39 (-0·07–0·85)
Arora 2021	290	10·53	1·73	210	8·95	1·53	4·36%	1·58 (1·29–1·86)
Barola 2018	231	10·00	2·70	141	9·20	2·40	4·03%	0·80 (0·27–1·33)
Baruah 2017	94	9·34	2·28	654	9·08	2·10	4·09%	0·26 (-0·23–0·75)
Bochanen 2021	92	7·50	1·10	54	7·40	1·20	4·23%	0·10 (-0·29–0·49)
Frid 2016	2205	8·85	2·70	4795	8·30	1·90	4·48%	0·55 (0·43–0·67)
Gentile 2019	169	9·20	1·60	127	8·10	2·30	4·12%	1·10 (0·63–1·57)
Gentile 2020	718	9·60	1·10	509	7·50	1·10	4·48%	2·10 (1·98–2·22)
Gentile 2021	360	8·00	1·20	420	7·70	1·30	4·45%	0·30 (0·12–0·48)
Gentile 2022	487	8·60	1·60	673	7·30	1·00	4·46%	1·30 (1·14–1·46)
Gupta 2018	97	9·62	2·13	42	9·84	2·66	3·32%	-0·22 (-1·13–0·69)
Gunhan 2022	98	8·50	1·70	247	9·30	7·80	3·09%	-0·80 (-1·83–0·23)
Hajheydari 2011	35	9·50	2·20	185	8·70	1·90	3·57%	0·80 (0·02–1·58)
Hauner 1996	66	8·90	1·80	213	8·80	1·70	4·09%	0·10 (-0·39–0·59)
Ji 2014	134	7·87	1·53	246	8·17	4·41	3·89%	-0·30 (-0·91–0·31)
Ji 2017	213	8·20	1·80	188	7·70	1·50	4·32%	0·50 (0·18–0·82)
Kamrul-Hasan 2020	78	10·00	2·20	769	9·50	2·00	4·06%	0·50 (-0·01–1·01)
Kumar 2021	79	9·12	2·53	8	8·68	1·39	2·93%	0·44 (-0·67–1·55)
Luo 2021	270	8·63	1·76	46	7·42	1·73	4·00%	1·21 (0·67–1·75)
Omar 2011	62	8·50	2·00	51	8·50	2·30	3·52%	0·00 (-0·80–0·80)
Pahuja 2019	65	8·30	x	31	7·90	x	3·79%	0·40 (-0·26–1·06)
Pozzouli 2018	151	7·70	1·40	202	7·70	1·30	4·36%	0·00 (-0·29–0·29)
Singha 2021	46	9·00	2·60	45	7·70	1·10	3·50%	1·30 (0·48–2·12)
Strollo 2016	298	8·30	1·20	89	7·50	1·10	4·38%	0·80 (0·53–1·07)
Thewjitcharoen 2020	149	7·80	1·50	251	7·90	1·70	4·32%	-0·10 (-0·42–0·22)
Total							**100%**	**0·55 (0·23–0·87)**

Test for heterogeneity:
Q=637·11, df=24 (p<0·0001), I²=96·23%

Test overall effect:
Z=3·35 (p<0·0008)

−1·6   −0·8   0   0·8   1·6
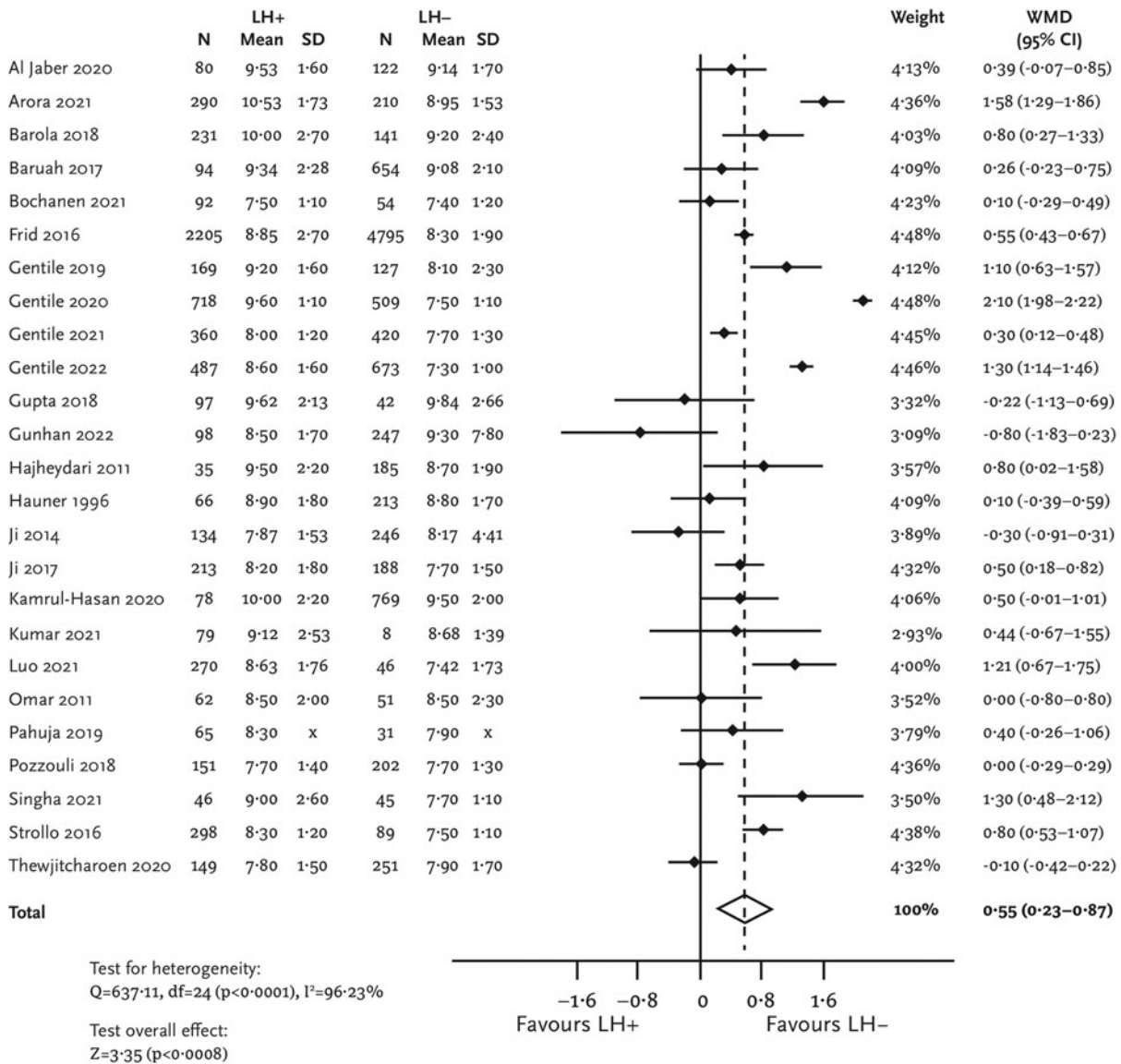Favours LH+   Favours LH−

FIG. 3. Forest plot for HbA1c.

HbA1c, and the total daily insulin dose (Supplementary Figs. S35–S37). However, only a few identified studies were published before 2014.

Based on subgroup analyses, we noticed that the impact of lipohypertrophy on the prevalence of unexplained hypoglycemia and uncontrolled glycemia was slightly more pronounced in individuals with T2DM than in those with T1DM; however, no significant interaction between subgroups was observed ($P > 0.05$). In contrast, we reported a significant interaction for a greater impact of lipohypertrophy on the total daily insulin dose in the T2DM subgroup compared with T1DM ($P = 0.013$).

We also found that in studies reporting lipohypertrophy measured by ultrasonography, the association with unexplained hypoglycemia, HbA1c values, and total daily insulin dose was more substantial than in those with only clinical assessment of lipohypertrophy ($P < 0.05$). Regarding the geographical region, random interactions resulting from the imbalance in the number of studies in particular subgroups

were noticed for unexplained hypoglycemia and the total daily insulin dose. Similarly, inconsistent results were reported for the impact of the diabetes duration. All subgroup analyses are presented in the Supplementary Appendix SA1 (Supplementary Figs. S14–S34).

No publication bias was identified for analyzed outcomes (Supplementary Figs. S38–S39).

Discussion

Our systematic review identified 37 studies comparing glycemic control parameters and insulin dosing in patients with and without lipohypertrophy. We performed meta-analyses with a satisfactory number of studies only for four outcomes (HbA1c, uncontrolled glycemia, unexplained hypoglycemia, and total daily insulin dose). Other endpoints stated in the protocol (e.g., hyperglycemia and continuous glucose monitoring) were available in only a few studies, limiting the possibility of conducting a reliable meta-
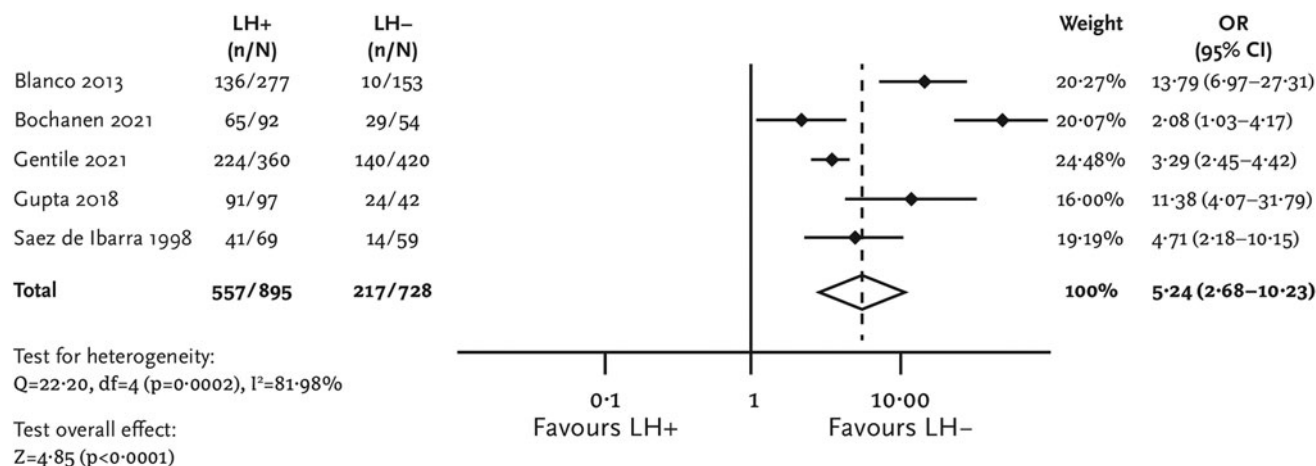
	LH+ (n/N)	LH- (n/N)		Weight	OR (95% CI)
Blanco 2013	136/277	10/153		20·27%	13·79 (6·97–27·31)
Bochanen 2021	65/92	29/54		20·07%	2·08 (1·03–4·17)
Gentile 2021	224/360	140/420		24·48%	3·29 (2·45–4·42)
Gupta 2018	91/97	24/42		16·00%	11·38 (4·07–31·79)
Saez de Ibarra 1998	41/69	14/59		19·19%	4·71 (2·18–10·15)
Total	557/895	217/728		100%	5·24 (2·68–10·23)

Test for heterogeneity:
Q=22·20, df=4 (p=0·0002), I²=81·98%

Test overall effect:
Z=4·85 (p<0·0001)

0·1 Favours LH+   1   10·00 Favours LH−

FIG. 4. Forest plot for glycemic variability.

analysis. Nonetheless, we were able to collect sufficient data to determine the possible relationship between lipohypertrophy and glycemic control.

Our results showed that all primary outcomes regarding glycemic control were significantly worse in patients with lipohypertrophy than those without lipohypertrophy. Episodes of unexplained hypoglycemia, uncontrolled glycemia, and glycemic variability were more prevalent in patients with lipohypertrophy than in a control group. In addition, those with confirmed lipohypertrophy also used higher insulin doses. Although these results suggest that lipohypertrophy is associated with poorer glycemic control and higher insulin doses, we cannot draw an unequivocal causal conclusion. Nearly all of the included studies were designed as cross-sectional without any follow-up.

Therefore, we cannot rule out that there are other causal factors affecting both the development of lipohypertrophy,

poor glycemic control, and higher doses of insulin. However, available data from studies evaluating the impact of educational programs on proper insulin injection techniques, with avoidance of injections into lipohypertrophy areas, indicate the direct involvement of lipohypertrophy in worsening glycemic control and excessive insulin dosing.

Wang et al.[56] reported that a 3-month intensive training on insulin injection technique in patients with lipohypertrophy resulted in a significant and clinically relevant decrease of mean HbA1c by 0.60%, fasting plasma glucose by 1.20 mmol/L, 2h postprandial plasma glucose by 1.70 mmol/L without increasing the insulin dosage. Indicators of glycemic variability, hyperglycemic and hypoglycemic events were also markedly decreased. These meaningful results were further confirmed by a randomized controlled trial conducted by the AMD-OSDI Study Group,[57] in which 318 patients with lipohypertrophy were assigned either to the intervention
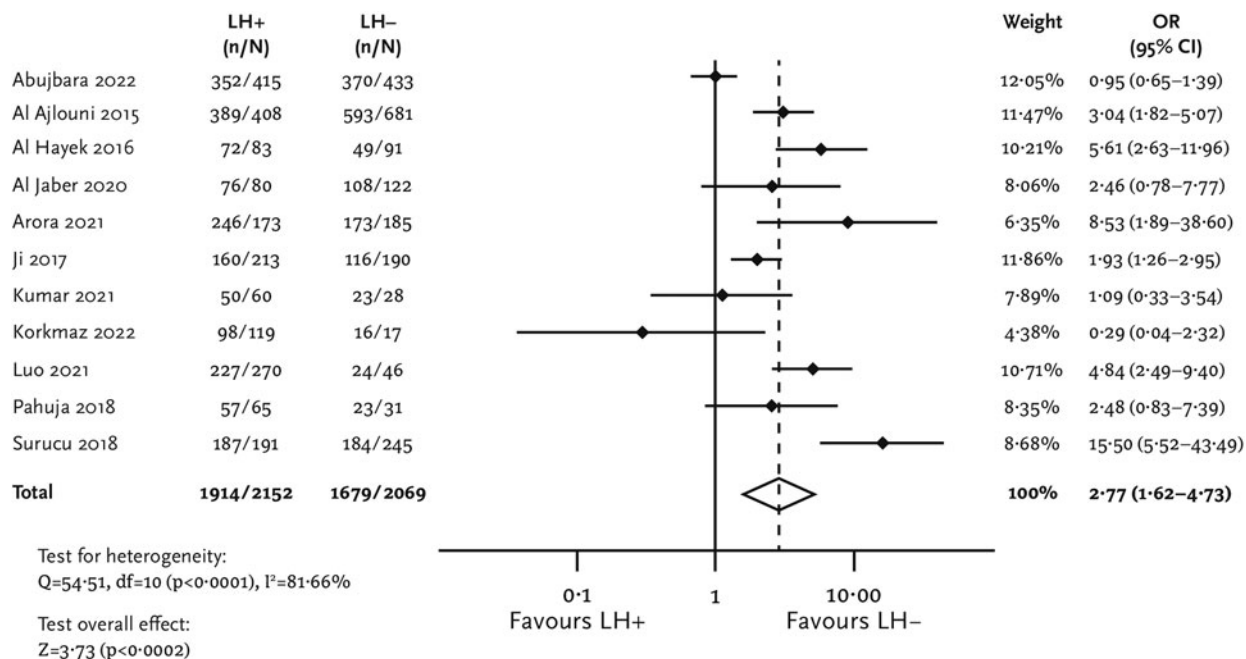
	LH+ (n/N)	LH- (n/N)		Weight	OR (95% CI)
Abujbara 2022	352/415	370/433		12·05%	0·95 (0·65–1·39)
Al Ajlouni 2015	389/408	593/681		11·47%	3·04 (1·82–5·07)
Al Hayek 2016	72/83	49/91		10·21%	5·61 (2·63–11·96)
Al Jaber 2020	76/80	108/122		8·06%	2·46 (0·78–7·77)
Arora 2021	246/173	173/185		6·35%	8·53 (1·89–38·60)
Ji 2017	160/213	116/190		11·86%	1·93 (1·26–2·95)
Kumar 2021	50/60	23/28		7·89%	1·09 (0·33–3·54)
Korkmaz 2022	98/119	16/17		4·38%	0·29 (0·04–2·32)
Luo 2021	227/270	24/46		10·71%	4·84 (2·49–9·40)
Pahuja 2018	57/65	23/31		8·35%	2·48 (0·83–7·39)
Surucu 2018	187/191	184/245		8·68%	15·50 (5·52–43·49)
Total	1914/2152	1679/2069		100%	2·77 (1·62–4·73)

Test for heterogeneity:
Q=54·51, df=10 (p<0·0001), I²=81·66%

Test overall effect:
Z=3·73 (p<0·0002)

0·1 Favours LH+   1   10·00 Favours LH−

FIG. 5. Forest plot for uncontrolled glycemia (HbA1c >7%).

	LH+			LH−			Weight	WMD (95% CI)
	N	Mean	SD	N	Mean	SD		
Al-Jaber 2020	80	77·33	32·70	122	58·95	35·00	3·25%	18·38 (8·90–27·86)
Barola 2018	231	38·30	16·90	141	44·80	19·20	5·72%	-6·50 (-10·35--2·65)
Baruah 2017	94	35·51	18·45	654	32·95	18·21	5·66%	2·56 (-1·42–6·54)
Blanco 2013	277	56·00	26·90	153	41·00	24·10	5·20%	15·00 (10·04–19·96)
Bochanen 2021	92	69·00	44·20	54	50·80	30·80	2·42%	18·20 (5·99–30·41)
Cunningham 2013	28	54·30	33·10	27	44·90	18·40	2·00%	9·40 (-4·69–23·49)
Frid 2016	2192	55·20	33·00	4889	45·10	31·50	6·52%	10·10 (8·46–11·74)
Gentile 2019	169	35·50	8·80	127	32·80	9·70	6·38%	2·70 (0·55–4·85)
Gentile 2020	718	54·90	8·20	509	42·30	10·00	6·64%	12·60 (11·54–13·66)
Gentile 2021	360	49·00	24·00	420	43·00	27·00	5·83%	6·00 (2·42–9·58)
Gentile 2022	487	65·50	10·60	673	53·60	9·50	6·62%	11·90 (10·72–13·08)
Gunhan 2022	98	119·00	96·00	247	95·00	61·00	1·12%	24·00 (3·53–44·47)
Gupta 2018	97	42·87	18·57	42	40·37	14·11	4·87%	2·50 (-3·15–8·15)
Hauner 1996	66	49·00	16·00	213	45·00	15·00	5·49%	4·00 (-0·35–8·35)
Kumar 2021	79	58·82	25·16	9	44·78	23·45	1·61%	14·04 (-2·25–30·33)
Luo 2021	270	33·09	15·60	46	30·43	13·35	5·52%	2·66 (-1·62–6·94)
Ji 2017	213	38·10	20·10	188	27·10	14·30	5·92%	11·00 (7·61–14·39)
Pahuja 2019	64	43·97	x	29	33·55	x	3·45%	10·42 (1·50–19·34)
Pozzuoli 2017	151	48·80	25·90	202	37·80	21·40	5·14%	11·00 (5·92–16·08)
Strollo 2016	298	49·00	18·00	89	41·00	19·00	5·44%	8·00 (3·55–12·45)
Thewjitcharoen 2020	149	43·00	24·00	251	41·00	25·00	5·21%	2·00 (-2·94–6·94)
Total							100%	7·68 (5·31–10·06)

Test for heterogeneity:
Q=213·43, df=20 (p<0·0001), I²=90·63%

Test overall effect:
Z=6·34 (p<0·0001)

−30 −15 0 15 30
Favours LH+   Favours LH−

FIG. 6. Forest plot for daily insulin dose.

group receiving appropriate injection technique education or to the control group without education.

After a 6-month follow-up, HbA1c values, glycemic variability, and episodes of severe and symptomatic hypoglycemia were significantly decreased in the intervention group compared with the control group. In addition, insulin doses in the intervention group decreased by nearly 21%, suggesting that improvement in injection technique and its impact on lipohypertrophy allows for a reduction in insulin consumption. Notably, the benefits associated with educating patients with lipohypertrophy on injection technique are not only limited to improving health outcomes but also result in cost savings in diabetic care, including insulin costs and treatment of diabetes complications.[55] Obtained results indicate the significance of the issue of lipohypertrophy and the necessity to adhere to FITTER guidelines regarding proper injection technique, including the importance of avoiding injections in areas affected by lipohypertrophy, proper site rotation, and needle single-use.[9]

Our research has some limitations that cannot be overcome, which result mainly from the low reliability of data pooled in meta-analyses. The studies included in this meta-analysis exhibited varying risks of bias and quality of reported outcomes. In many studies, comprehensive information on the research methodology and statistical analysis assumptions was not provided. Errors in reporting patient numbers and events also occurred,[28,52] which made it impossible to cumulate these data for specific endpoints. Another issue observed was a high heterogeneity for almost all analyzed outcomes ($I^2 > 80\%$).

We could not establish the source of heterogeneity since the studies included in the meta-analysis were diverse in many factors simultaneously. At the same time, based on aggregated data, we could only investigate one factor in subgroup analyses. According to the protocol, we aimed to obtain a result on the effect of lipohypertrophy on glycemic control, regardless of the type of diabetes, patients' age, treatment history, and different diabetic management standards of care in various geographical regions.

In addition, differences in the definition and diagnosis of lipohypertrophy and analyzed outcomes between studies could have influenced the high heterogeneity of results. For example, in some studies, the definition of lipohypertrophy also included patients with lipoatrophy, and the diagnosis could be based on either ultrasonographic examination or solely visually and by palpation. To eliminate this potential

bias, if possible, we excluded data for patients with lipoatrophy from the analysis. In other cases, patients with lipoatrophy constituted a small proportion of the entire lipohypertrophy group, so including their data should not have significantly affected the meta-analysis results.

We also performed subgroup analyses regarding the type of lipohypertrophy measurement. Interestingly, our results showed that the negative impact of lipohypertrophy on glycemic control was markedly higher in those with lipohypertrophy confirmed by ultrasound imaging compared with those with clinical assessment alone. This result may suggest that patients with subclinical lipohypertrophy, often unaware of their condition, are particularly vulnerable to glycemic fluctuations due to insulin injections into lipohypertrophy areas. At the same time, adequately educated patients with visible lipohypertrophy may avoid administering insulin into lipohypertrophic nodules.

Unfortunately, due to insufficient reporting in the studies, no analysis considering the proportion of diabetic patients with lipohypertrophy who injected insulin into affected areas could be performed. Therefore, the observed heterogeneity in our meta-analyses may also result from the inability to consider the actual percentage of patients injecting insulin into lipohypertrophy. Nonetheless, in light of these findings, it may be worth considering the introduction of routine ultrasonographic assessments in both clinical practice and trials as a more sensitive diagnostic method.

Other subgroup analyses indicate that the impact of lipohypertrophy on glycemic control was slightly more pronounced in T2DM than in those in T1DM. One possible explanation is that patients with T1DM are often better educated in injection technique and the negative consequences of lipohypertrophy due to the usual longer duration of insulin therapy. In contrast, the frequently coexisting obesity in patients with T2DM may affect the overlook of skin changes.

The pathophysiology of lipohypertrophy in patients with diabetes has not been fully elucidated, but some authors suggest that it may result not only from the lipogenic properties of insulin, promoting the growth of fat cells but also from mechanical damage to subcutaneous tissue through repeated and improper injections in the same location.[9] The rationale for including glucagon-like peptide 1 receptor agonists (GLP-1-RAs) in the meta-analysis was based on the observation that some studies reported the occurrence of lipohypertrophy in patients using GLP-1-RA.[58]

Despite a comprehensive literature review, we found no scientific evidence regarding the potential link between lipohypertrophy and glycemic control in patients receiving GLP-1 analogs. Only one study included in the systematic review[9] involved patients using GLP-1 receptor agonists, but they accounted for <2% of all study participants, and no subgroup analysis was available for them. Thus, there is a significant evidence gap for this patient group, and further research should focus on assessing the occurrence of lipohypertrophy and its consequences in patients treated with other than insulin subcutaneous antihyperglycemic medications.

Conclusions

The meta-analysis results indicate that lipohypertrophy is associated with poorer glycemic control and higher insulin consumption. Clinicians and health care providers should be aware that lipohypertrophy is not only a cosmetic issue but also a clinically relevant topic. Routine screening for lipohypertrophy and intensive patient education on the proper insulin injection technique, including site rotation and needle single-use, may have a beneficial effect on better diabetes control, insulin dosing, and prevention of long-term complications of the disease.

Authors' Contributions

A.S.-T. and M.M. performed a systematic search, data extraction, and statistical analyses. All authors were involved in protocol preparation, data interpretation, article writing, and editing. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Author Disclosure Statement

Funding Information

Supplementary Material

Supplementary Appendix SA1

References

1. Abu Ghazaleh H, Hashem R, Forbes A, et al. A systematic review of ultrasound-detected lipohypertrophy in insulin-exposed people with diabetes. Diabetes Ther 2018;9(5): 1741–1756; doi: 10.1007/s13300-018-0472-7

2. 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(2):259–267; doi: 10.1007/s13300-016-0161-3

3. Barola A, Tiwari P, Bhansali A, et al. Insulin-related lipohypertrophy: Lipogenic action or tissue trauma? Front Endocrinol 2018;9:638; doi: 10.3389/fendo.2018.00638

4. Blanco M, Hernández MT, Strauss KW, et al. Prevalence and risk factors of lipohypertrophy in insulin-injecting patients with diabetes. Diabetes Metab 2013;39(5):445–453; doi: 10.1016/j.diabet.2013.05.006

5. Baruah M, Kalra S, Bose S, et al. An audit of insulin usage and insulin injection practices in a large Indian cohort. Indian J Endocr Metab 2017;21(3):443–452; doi: 10.4103/ijem.IJEM_548_16

6. Gentile S, Guarino G; AMD-OSDI Study Group, et al. Bruising: A neglected, though patient-relevant complication of insulin injections coming to light from a real-life nationwide survey. Diabetes Ther 2021;12(4):1143–1157; doi: 10.1007/s13300-021-01026-w

7. Elsayed S, Soliman AT, De Sanctis V, et al. Insulin-induced lipodystrophy and predisposing factors in children and adolescents with type 1 diabetes mellitus (T1DM) in a tertiary care Egyptian center. Acta Biomed 2023;94(3): e2023078; doi: 10.23750/abm.v94i3.14117

8. Lin Y, Lin L, Wang W, et al. Insulin-related lipohypertrophy: Ultrasound characteristics, risk factors, and impact of glucose fluctuations. Endocrine 2022;75(3):768–775; doi: 10.1007/s12020-021-02904-w

9. Frid AH, Kreugel G, Grassi G, et al. New insulin delivery recommendations. Mayo Clin Proc 2016;91(9):1231–1255; doi: 10.1016/j.mayocp.2016.06.010

10. Perciun R. Ultrasonographic aspect of subcutaneous tissue dystrophies as a result of insulin injections. Med Ultrason 2010;12(2):104–109.

11. Xu X-H, Carvalho V, Wang X-H, et al. Lipohypertrophy: Prevalence, clinical consequence, and pathogenesis. Chin Med J 2021;134(1):47–49; doi: 10.1097/CM9.0000000000000970

12. Gentile G, Strollo F. Factors hindering correct identification of unapparent lipohypertrophy. J Diabetes Metab Disord Control 2016;3(2):42–47; doi: 10.15406/jdmdc.2016.03.00065

13. Wang K, Zhang S, Liu C, et al. A meta-analysis and meta-regression on the prevalence of lipohypertrophy in diabetic patients on insulin therapy. Therapies 2021;76(6):617–628; doi: 10.1016/j.therap.2021.04.002

14. Volkova NI, Davidenko IY. Clinical significance of lipohypertrophy without visual and palpable changes detected by ultrasonography of subcutaneous fat. Ter Arkh 2019; 91(4):62–66; doi: 10.26442/00403660.2019.04.000128

15. Volkova N, Davidenko I, Rudakova J, et al. Insulin-induced lipohypertrophy diagnostics in diabetic patients: Subcutaneous fat ultrasonography. Endocrine Abstracts 2015; 37 EP351; doi: 10.1530/endoabs.37.EP351

16. Gentile S, Guarino G, Della Corte T, et al. Why do so many people with type 2 diabetes who take insulin have lipohypertrophy? Fate or educational deficiencies? Diabetes Ther 2023;14(1):179–191; doi: 10.1007/s13300-022-01341-w

17. Bochanen N, Decochez K, Heleu E, et al. Lipohypertrophy Monitoring Study (LIMO): Effect of single use of 4 mm pen needles combined with education on injection site rotation on glycaemic control: Confirmation of an unpleasant truth. Diabet Med 2022;39(1):e14672; doi: 10.1111/dme.14672

18. Kamrul-Hasan A, Amin MN, Gaffar MAJ, et al. Insulin injection practice and injection complications—Results from the Bangladesh Insulin Injection Technique Survey. Eur Endocrinol 2020;16(1):41–48; doi: 10.17925/EE.2020.16.1.41

19. Johansson U-B, Amsberg S, Hannerz L, et al. Impaired absorption of insulin aspart from lipohypertrophic injection sites. Diabetes Care 2005;28(8):2025–2027; doi: 10.2337/diacare.28.8.2025

20. Famulla S, Hövelmann U, Fischer A, et al. Insulin injection into lipohypertrophic tissue: Blunted and more variable insulin absorption and action and impaired postprandial glucose control. Diabetes Care 2016;39(9):1486–1492; doi: 10.2337/dc16-0610

21. Tsadik AG, Atey TM, Nedi T, et al. Effect of insulin-induced lipodystrophy on glycemic control among children and adolescents with diabetes in Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia. J Diabetes Res 2018; 2018:1–7; doi: 10.1155/2018/4910962

22. Pozzuoli GM, Laudato M, Barone M, et al. Errors in insulin treatment management and risk of lipohypertrophy. Acta Diabetol 2018;55(1):67–73; doi: 10.1007/s00592-017-1066-y

23. Ji L, Sun Z, Li Q, et al. Lipohypertrophy in China: Prevalence, risk factors, insulin consumption, and clinical impact. Diabetes Technol Ther 2017;19(1):61–67; doi: 10.1089/dia.2016.0334

24. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. BMJ 2021;372:n71; doi: 10.1136/bmj.n71

25. Moola S, Munn Z, Tufanaru C, et al. Chapter 7: Systematic Reviews of Etiology and Risk. In: Joanna Briggs Institute Reviewer's Manual. (Aromataris E, Munn Z, eds.) JBI Manual for Evidence Synthesis. The Joanna Briggs Institute: 2017. Available from: https://synthesismanual.jbi.global; doi: 10.46658/JBIMES-20-08

26. Tufanaru C, Munn Z, Aromataris E, et al. Chapter 3: Systematic Reviews of Etiology and Risk. In: Joanna Briggs Institute Reviewer's Manual. (Aromataris E, Munn Z, eds.) The Joanna Briggs Institute: 2017. Available from: https://synthesismanual.jbi.global; doi: 10.46658/JBIMES-20-04

27. Abujbara M, Khreisat EA, Khader Y, et al. Effect of insulin injection techniques on glycemic control among patients with diabetes. Int J Gen Med 2022;15:8593–8602; doi: 10.2147/IJGM.S393597

28. Al Ajlouni M, Abujbara 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(2):e20776; doi: 10.5812/ijem.20776

29. AlJaber AN, Sales I, Almigbal TH, et al. The prevalence of lipohypertrophy and its associated factors among Saudi patients with type 2 diabetes mellitus. J Taibah Univ Med Sci 2020;15(3):224–231; doi: 10.1016/j.jtumed.2020.03.006

30. Arora S, Agrawal NK, Shanthaiah DM, et al. Early detection of cutaneous complications of insulin therapy in type 1 and type 2 diabetes mellitus. Prim Care Diabetes 2021; 15(5):859–864; doi: 10.1016/j.pcd.2021.06.004

31. Cunningham MT, McKenna M. Lipohypertrophy in insulin-treated diabetes: Prevalence and associated risk factors. J Diabetes Nurs 2013;17(9):340–343.

32. Frid AH, Hirsch LJ, Menchior AR, et al. Worldwide injection technique questionnaire study: Injecting complications and the role of the professional. Mayo Clin Proc 2016; 91(9):1224–1230; doi: 10.1016/j.mayocp.2016.06.012

33. Frid AH, Hirsch LJ, Menchior AR, et al. Worldwide injection technique questionnaire study: Population parameters and injection practices. Mayo Clin Proc 2016;91(9): 1212–1223; doi: 10.1016/j.mayocp.2016.06.011

34. Anonymous. ITQ Survey Data Mayo. Available from: https://public.tableau.com/profile/adam.yeung#!/vizhome/ ITQsurveydataMayo/START [Last accessed: March 2, 2020].

35. Gentile S, Strollo F, Satta E, et al. Insulin-related lipohypertrophy in hemodialyzed diabetic people: A multicenter observational study and a methodological approach. Diabetes Ther 2019;10(4):1423–1433; doi: 10.1007/s13300-019-0650-2

36. Gentile S, Guarino G; the AMD-OSDI Study Group on Injection Techniques and Nefrocenter Research and Nyx Start-Up Study Group, et al. Insulin-induced skin lipohypertrophy in type 2 diabetes: A multicenter regional survey in Southern Italy. Diabetes Ther 2020;11(9):2001–2017; doi: 10.1007/s13300-020-00876-0

37. Gunhan H, Elbasan O, Imre E, et al. Lipodystrophy frequency according to insulin treatment regimen in type 2 diabetic patients: Is insulin injection frequency matters in analog insulin era? Acta Endo (Buc) 2022;18(2):202–208; doi: 10.4183/aeb.2022.202

38. Gupta SS, Gupta KS, Gathe SS, et al. Clinical implications of lipohypertrophy among people with type 1 diabetes in India. Diabetes Technol Ther 2018;20(7):483–491; doi: 10.1089/dia.2018.0074

39. Hajheydari Z, Kashi Z, Akha O, et al. Frequency of lipodystrophy induced by recombinant human insulin. Eur Rev Med Pharmacol Sci 2011;15:1196–1201.

40. Hauner H, Stockamp B, Haastert B. Prevalence of lipohypertrophy in insulin-treated diabetic patients and predisposing factors. Exp Clin Endocrinol Diabetes 1996; 104(02):106–110; doi: 10.1055/s-0029-1211431

41. 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(6):1087–1093; doi: 10.1185/ 03007995.2014.895711

42. Ji L, Chandran A, Inocencio TJ, et al. The association between insurance coverage for insulin pen needles and healthcare resource utilization among insulin-dependent patients with diabetes in China. BMC Health Serv Res 2018;18(1):300; doi: 10.1186/s12913-018-3095-9

43. Korkmaz FN, Gökçay Canpolat A, Güllü S. Determination of insulin-related lipohypertrophy frequency and risk factors in patients with diabetes. Endocrinol Diabetes Nutr (Engl Ed) 2022;69(5):354–361; doi: 10.1016/j.endinu.2021.07.002

44. Kumar R, Gupta RD, Shetty S, et al. Lipohypertrophy in insulin injecting patients with diabetes mellitus: An under-recognized barrier for glycemic control. Int J Diabetes Dev Ctries 2021; 41(2):329–336; doi: 10.1007/s13410-020-00889-2

45. Luo D, Shi Y, Zhu M, et al. Subclinical lipohypertrophy— Easily ignored complications of insulin therapy. J Diabetes Complications 2021;35(3):107806; doi: 10.1016/j .jdiacomp.2020.107806

46. Nawaz A, Hasham MA, Shireen M, et al. Prevalence of lipohypertrophy and its associations in insulin-treated diabetic patients. Pak J Med Sci 2022;39(1):209–213; doi: 10 .12669/pjms.39.1.6134

47. Omar MA, El-Kafoury AA, El-Araby RI. Lipohypertrophy in children and adolescents with type 1 diabetes and the associated factors. BMC Res Notes 2011;4(1):290; doi: 10 .1186/1756-0500-4-290

48. Pahuja V, Punjot P, Fernandes G, et al. Exploring the factors associated with lipohypertrophy in insulin-treated type 2 diabetes patients in a tertiary care hospital in Mumbai, India. Int J Diabetes Dev Ctries 2019;39(3):426– 431; doi: 10.1007/s13410-019-00735-0

49. Saeed M, Aslam W, Ahmad M, et al. Frequency and risk factors of lipohypertrophy in insulin treated patients with diabetes: An experience from a tertiary care center in Multan. Med Forum Mon 2022;33(8):78–82.

50. Saez de Ibarra L, Gallego F. Factors related to lipohypertrophy in insulinltreated diabetic patients: Role of educational intervention. Pract Diabetes Int 1998;15(1):9–11.

51. Singha A, Bhattacharjee R, Dalal BS, et al. Associations of insulin-induced lipodystrophy in children, adolescents, and young adults with type 1 diabetes mellitus using recombinant human insulin: A cross-sectional study. J Pediatr Endocrinol Metab 2021;34(4):503–508; doi: 10.1515/jpem-2020-0556

52. Strollo F, Guarino G, Armentano V. Unexplained hypoglycaemia and large glycaemic variability: Skin lipohypertrophy as a predictive sign. Diabetes Res 2016;2(1):24–32.

53. Arda Sürücü H, OKurArslan H. Lipohypertrophy in individuals with type 2 diabetes: Prevalence and risk factors. J Caring Sci 2018;7(2):67–74; doi: 10.15171/jcs.2018.011

54. Thewjitcharoen Y, Prasartkaew H, Tongsumrit P, et al. Prevalence, risk factors, and clinical characteristics of lipodystrophy in insulin-treated patients with diabetes: An old problem in a new era of modern insulin. Diabetes Metab Syndr Obes 2020;13:4609–4620; doi: 10.2147/ DMSO.S282926

55. Gentile S, Guarino G, Della Corte T, et al. The economic burden of insulin injection-induced lipohypertophy. Role of education: The ISTERP-3 study. Adv Ther 2022;39(5): 2192–2207; doi: 10.1007/s12325-022-02105-5

56. Wang W, Tong Y, Chen Y, et al. Evaluation of ultrasound examination combined with intensive injection technique education on insulin-induced lipohypertrophy (LH) management: A prospective cohort study in China. Int J Diabetes Dev Ctries 2021;41(4):669–675; doi: 10.1007/s13410-021-00935-7

57. Gentile S, Guarino G; AMD-OSDI Study Group on Injection Technique, Nefrocenter Research and Nyx Start-Up, et al. Role of structured education in reducing lypodistrophy and its metabolic complications in insulin-treated people with type 2 diabetes: A randomized multicenter case–control study. Diabetes Ther 2021;12(5):1379–1398; doi: 10.1007/s13300-021-01006-0

58. Kirac C, Gonullu C, Baldane S, et al. Effect of vitamin D deficiency on the frequency of lipohypertrophy occurrence in patients with type 2 diabetes mellitus under injectable treatment. Turk J Endocrinol Metab 2020;24:184–188; doi: 10.25179/tjem.2020-74469

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