

Relationship between lipohypertrophy, glycemic control, and insulin dosing: a systematic meta-analysis

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Introduction

- 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.

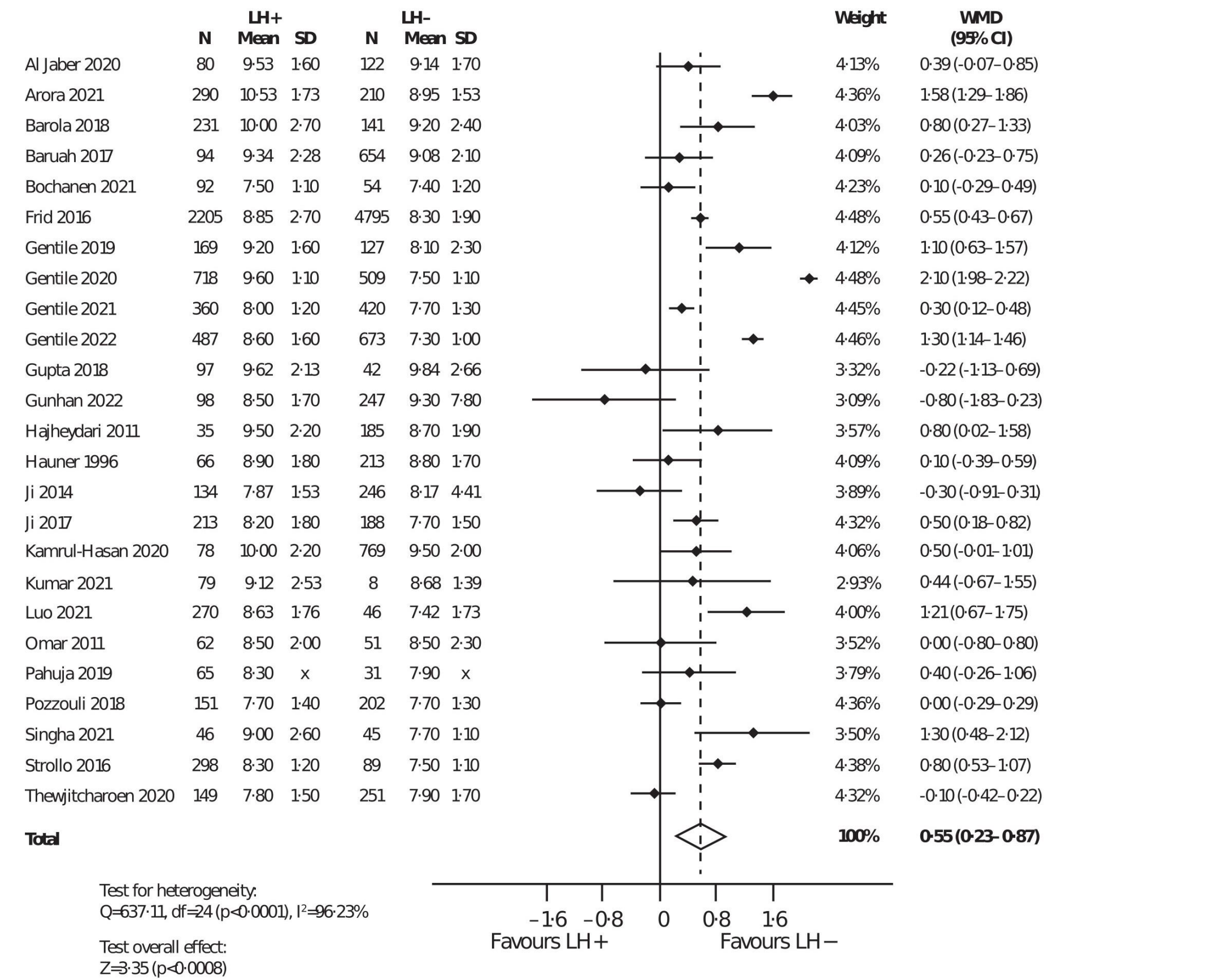
Methods

- 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, 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 (pOR) or mean differences (MD) with 95% confidence intervals (95% CI). This study was registered on PROSPERO (CRD42023393103).

Data Analysis

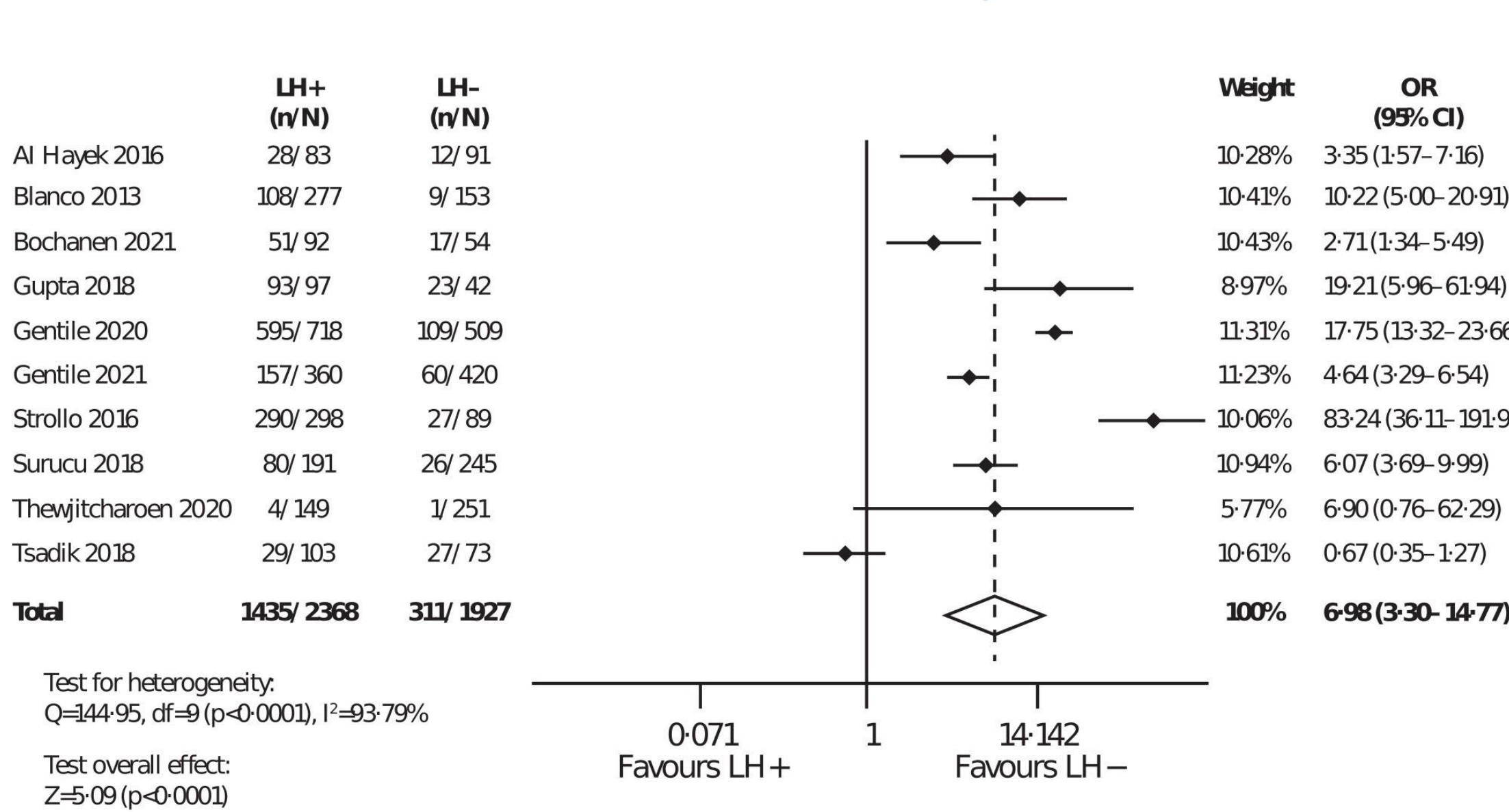
- Two reviewers (AST, MM) performed data extraction independently. All discrepancies between reviewers were discussed and resolved. Extracted items included the design of studies, baseline population characteristics, details of anti-hyperglycemic therapy, analyzed outcomes (HbA1c, glycemic variability, uncontrolled glycemia, or 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-sectional²¹ and quasi-experimental²² 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 (pOR) for the proportion of patients with an event or as mean differences (MD) for outcomes expressed by means and standard deviations (SD). All results were given with 95% confidence intervals (95% CI). We used a random model (DerSimonian & Laird) for data cumulation if significant between-study heterogeneity was observed (p-value for Cochran Q test <0.10 and I² >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 last ten years, to determine if the publication date impacted meta-analyses results. Subgroup and sensitivity analyses were performed only for outcomes, including at least ten studies in the primary meta-analyses. The risk of publication bias for meta-analysis of at least ten 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).

Forest plot: for Hb1 ac



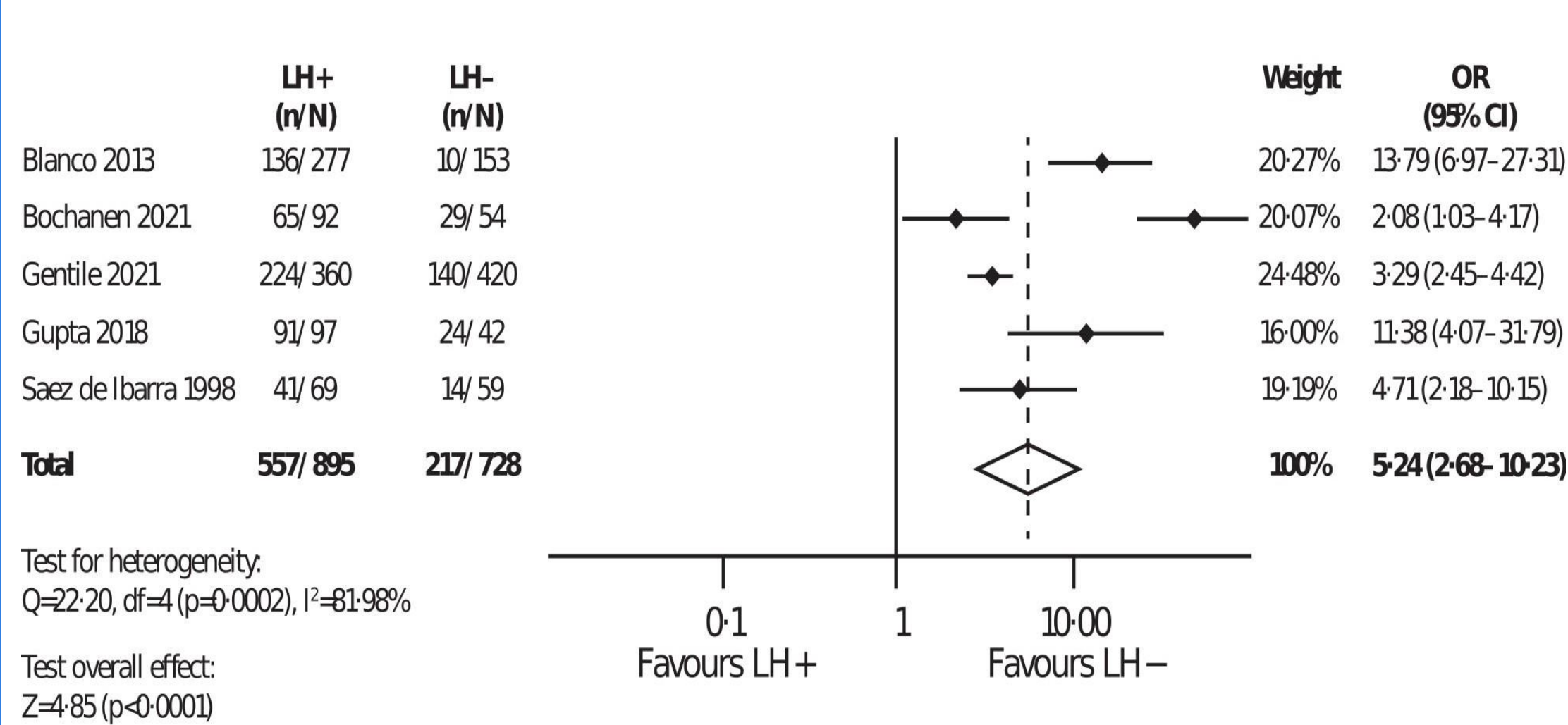
HbA1c levels were significantly higher in patients with lipohypertrophy compared to those without lipohypertrophy, with a mean difference in HbA1c of 0.55 % [95% CI: 0.23, 0.87] (favoring the LH- group as having lower HbA1c)

Forest Plot for Unexplained hypoglycemia



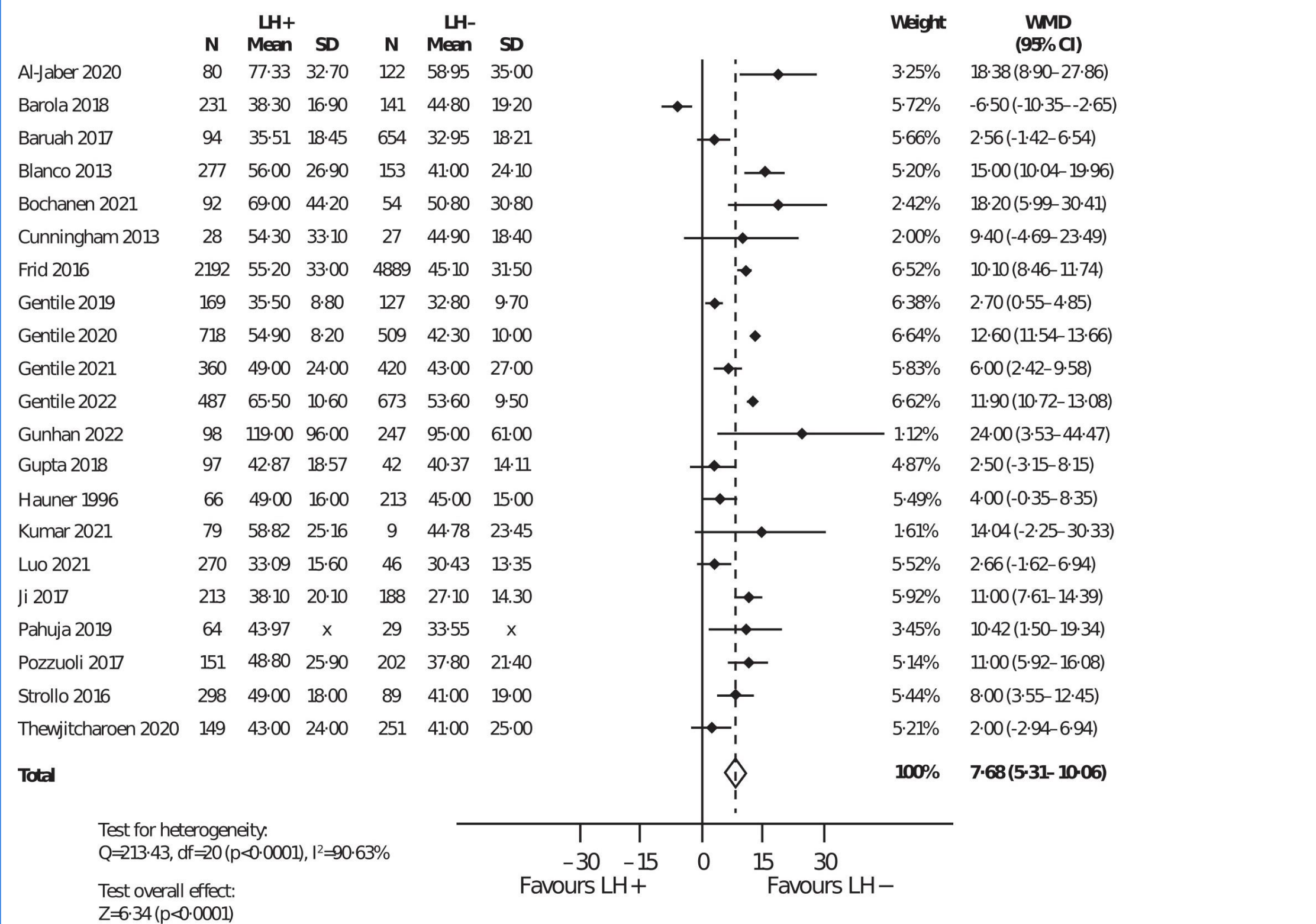
The prevalence of unexplained hypoglycemia was 7 times higher in patients with lipohypertrophy compared to those without lipohypertrophy, with an odds ratio of 6.98 [95% CI: 3.30; 14.77] (the results favor the LH- group with a lower prevalence of unexplained hypoglycemia).

Forest Plot for glycemic variability



The prevalence of glycemic variability was 5 times higher in the lipohypertrophy group compared to the group without lipohypertrophy, with an odds ratio of 5.24 [95% CI: 2.68; 10.23] (the results favor the LH- group with a lower prevalence of glycemic variability).

Forest plot for Total Daily Insulin Doses

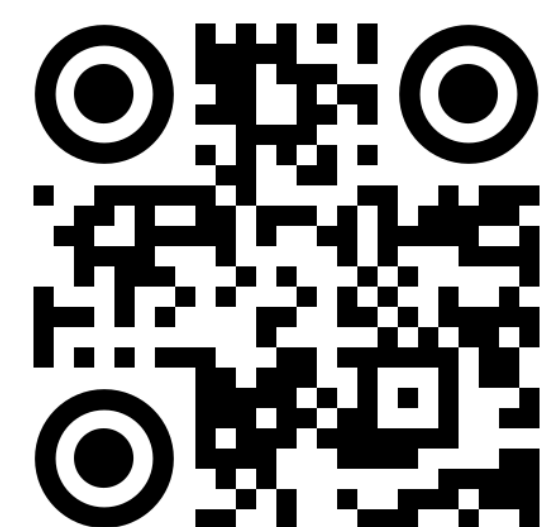


The daily insulin dose administered by patients with lipohypertrophy was on average 7.7 units higher than in patients without lipohypertrophy, with a mean difference of 7.68 IU [95% CI: 5.31; 10.06] (favoring the LH- group as having a lower insulin dose).

Key Findings

- The primary analysis showed that patients with lipohypertrophy were more likely to experience unexplained hypoglycemia (pOR [95% CI] = 6.98 [3.30–14.77]) and overall hypoglycemia (pOR [95% CI] = 6.65 [1.37–32.36]) compared with patients without lipohypertrophy.
- Patients with lipohypertrophy also had significantly higher values of HbA1c than those without lipohypertrophy (MD [95% CI] = 0.55 [0.23–0.87]). Uncontrolled glycemia, defined as HbA1c values >7%, was also more common among the lipohypertrophy group (pOR [95% CI] = 2.77 [1.62–4.73]). 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. Additionally, those with confirmed lipohypertrophy also used higher insulin doses.
- 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 to 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.
- These results suggest that overall glycemic control is worse in patients with lipohypertrophy than in those without this condition.

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Abbreviations

LH: lipohypertrophy
LH+: lipohypertrophy group
LH-: without lipohypertrophy

References

- 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.

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Disclosures

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