BMJ Open

Efficacy of education on injection technique for patients diagnosed with diabetes with lipohypertrophy: systematic review and meta-analysis

Masahiro Ichikawa [iD],[1] Tomoaki Akiyama,[1] Yasushi Tsujimoto,[2] Keisuke Anan,[3] Tadashi Yamakawa,[1] Yasuo Terauchi [iD] [4]

[1]Department of Endocrinology and Diabetes, Yokohama City University Medical Center, Yokohama, Japan
[2]Department of Nephrology and Dialysis, Kyoritsu Hospital, Kawanishi, Japan
[3]Department of Healthcare Epidemiology, Graduate School of Medicine and Public Health, Kyoto University, Kyoto, Japan
[4]Department of Endocrinology and Metabolism, Graduate School of Medicine, Yokohama City University School of Medicine, Yokohama, Japan

Correspondence to
Dr Masahiro Ichikawa;
t196009c@yokohama-cu.ac.jp

ABSTRACT

Objectives This study aimed to investigate the efficacy of providing education on injection technique to patients with diabetes with lipohypertrophy (LH).

Design We conducted a systematic review and meta-analysis.

Methods We included patients with diabetes who use insulin and have LH, and excluded patients without LH. We performed a literature search on CENTRAL, MEDLINE, EMBASE, ICTRP and ClinicalTrials.gov in November 2021 for randomised controlled trials (RCTs). We used the revised Cochrane Risk of Bias 2 tool to evaluate the risk of bias in each outcome in each study. We then pooled the data using a random-effects model and evaluated the certainty of evidence using the Grading of Recommendations, Assessment, Development and Evaluation approach.

Outcome measures The primary endpoints were change in total daily dose (TDD) of insulin, change in HbA1c levels and prevalence of hypoglycaemia.

Results We screened 580 records and included three RCTs (637 participants) in the meta-analysis. Education on injection technique may slightly increase the change of TDD of insulin (three studies, 637 participants: mean difference (MD) −6.26; 95% CI −9.42 to −3.10; p<0.001; I^2=38%; low certainty of evidence) and may have little to no effect on change in HbA1c but the evidence is very uncertain compared with that in the control group (three studies, 637 participants: MD −0.59; 95% CI −1.71 to 0.54; p=0.31; I^2=98%; very low certainty of evidence). Providing education about injection technique may have little to no effect on the prevalence of hypoglycaemia (three studies, 637 participants: risk ratio 0.44; 95% CI 0.06 to 3.13; p=0.41; I^2=90%; very low certainty of evidence).

Conclusions The present meta-analysis suggests that injection technique education may result in a slight reduction in the TDD of insulin. However, the effect of education on HbA1c, hypoglycaemia and cured LH is uncertain.

Protocol registration DOI: dx.doi.org/10.17504/protocols.io.btiinkce

Strengths and limitations of this study

► We conducted a comprehensive search and summarised the evidence for the effects of injection technique education.

► We used a prospective registered protocol, followed the Cochrane Handbook and Grading of Recommendations, Assessment, Development and Evaluation, selected a rigorous methodology and adhered to the reporting guidelines.

► The limitation of this study was the fact that we did not have sufficient data to perform a subgroup analysis and could not evaluate the long-term effects of education on injection technique.

estimated to die due to diabetes and its complications.[1] The number of patients with diabetes is expected to increase to 700 million by 2045.[1] Blood glucose control is important to prevent the complications of diabetes, and insulin therapy plays a key role in regulating blood glucose level in patients.[2] Insulin therapy is necessary for type 1 diabetes and type 2 diabetes and is estimated to be used in 7.5% of patients with type 2 diabetes.[3] Lipohypertrophy (LH), a side effect of long-term insulin injection, has been reported in 38% of patients with diabetes.[4] LH is caused by the thickening of adipose tissue localised to the site of insulin injection.[5 6]

Patients with LH face insulin variability because both insulin absorption and action become slow.[4 7 8] Moreover, the risk of unexpected hypoglycaemia has been noted in patients with LH.[7] Previous studies have suggested that providing proper education on injection techniques (IT) may reduce HbA1c levels and/or total daily dose (TDD) of insulin.[9–13] IT education includes rotating the injection sites properly, avoiding needle reuse and avoiding injecting into the site of
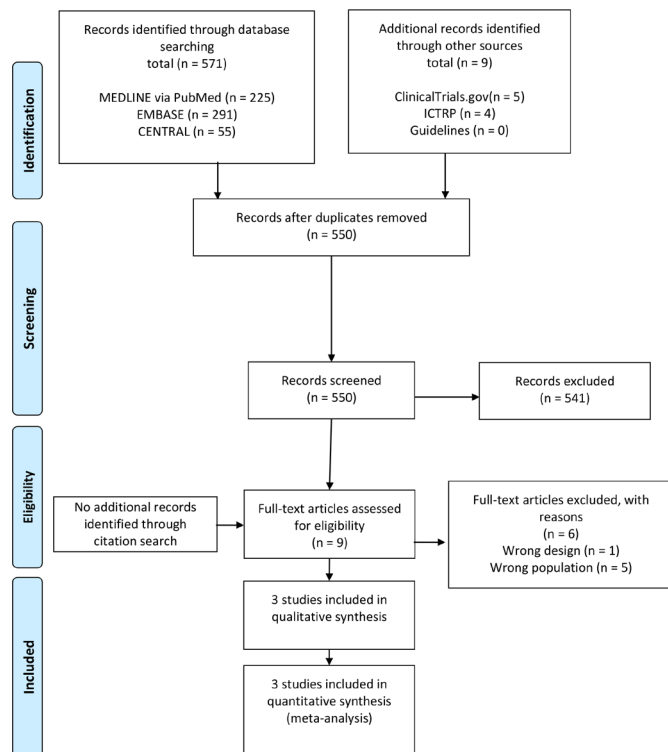
INTRODUCTION

There has been a continuous increase in the number of patients with diabetes worldwide, and diabetes has become a major public health problem, with 4.2 million adults

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

LH.[5] It is also recommended to use a 4 mm long needle to avoid injection into the muscle.[5 14]

To the best of our knowledge, there has been no systematic investigation on the effects of providing education about IT on the TDD of insulin, HbA1c levels and hypoglycaemia in patients with diabetes with LH. Therefore, we aimed to perform a systematic review and meta-analysis to determine the efficacy of providing education on the IT to patients with diabetes with LH.

METHODS
Eligibility criteria
We conducted this systematic review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines,[15] and the checklist is shown in the online supplemental table S1. We conducted a systematic review investigating the effects of IT on patients with type 1 or type 2 diabetes who use insulin and have LH, and included individual, cluster and cross-over randomised trials. We did not limit the inclusion to languages or countries. We included published and unpublished papers, conference abstracts, letters and all other types of papers. We excluded observational studies and non-randomised controlled trials (RCTs). We did not exclude studies because of the observation period or year of publication.

We included patients with type 1 or type 2 diabetes who had been receiving insulin injections for at least 1 year, with LH, 18 years old and above, any sex, no HbA1c restriction and no education about LH within the past 6 months. LH diagnosis was made by a physician, nurse

or investigators when it was clinically visible, palpable or visible on ultrasound.[4] We accepted any number of insulin injections per day or needle size for insulin injections.

We excluded pregnant women, patients who wished to become pregnant, lactating women and patients taking medications that may cause LH (antiretroviral or corticosteroid therapy).

Information sources
Search strategy
We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE using PubMed and EMBASE using ProQuest Dialog on 11 November 2021. We also searched the WHO International Clinical Trials Registry Platform (ICTRP) Search Portal and Clinical-Trials.gov on 11 November 2021 for ongoing or unpublished trials. The search strategies are presented in the online supplemental table S2. We checked the reference lists of the studies, including international guidelines, and identified the reference lists of eligible studies and articles citing eligible studies.

Selection process
Two independent reviewers (MI and TA) screened the titles and abstracts, followed by an assessment of eligibility based on the full texts. We contacted the original authors if the relevant data were missing. Disagreements between the two reviewers were resolved by discussion, and if this was not possible, a third reviewer (YTs or KA) became an arbiter.

Data collection process
Two reviewers (MI and TA) independently extracted data from included studies using a standardised data collection form. Disagreements were resolved by discussion, and if this was not possible, a third reviewer (YTs or KA) became an arbiter. We conducted up to two author queries by email to obtain the relevant data from the researchers.

Data items
The primary endpoints were changes in insulin TDD and HbA1c levels, and the prevalence of hypoglycaemia. The change in insulin TDD was defined as the change in TDD from baseline, and the duration was the longest follow-up period after 3 months. The change in HbA1c levels was defined as the change in HbA1c from baseline, and the duration was the longest follow-up period after 3 months. Hypoglycaemia was defined as one or more hypoglycaemic symptoms (palpitations, fatigue, sweating, strong hunger, dizziness, tremors, etc) and a blood glucose level below 60 mg/dL.[7] We accepted hypoglycaemia as defined by the original authors. Duration was the longest follow-up period after 3 months. The secondary endpoints were changes in the proportion of patients with cured LH and all adverse events. The definition of change in the proportion of patients with cured LH was the same as that of the original paper, and the duration was the longest follow-up period after 3 months. All adverse events were the same as those defined in the original study.

Table 1 Characteristics of the included studies

Study	Methods	Subject characteristics	Intervention details	Reported outcome of interest
Campinos et al[12]	Location: France Sample size: 123 Detection method of LH: visible and/or palpable LH determined by nurses	Age (years): 52.8±15.1 (IT), 51.4±16.4 (C) Male (%): 70.7 Number of T1DM/T2DM individuals: 66/57 Estimated diabetes duration (years): 19.8±11.5 (IT), 16.3±9.2 (C) Insulin treatment duration (years): 14.8±12.8 (IT), 12.5±10 (C)	IT: reducing insulin doses initially by 20%, instructing to rotate within injection sites, foregoing needle reuse, stopping injecting into the LH site and switching to 4 mm needles. C: standard care. All participants received information about optimal IT and LH at baseline.	Change in TDD of insulin from baseline. Change in HbA1c levels from baseline. Hypoglycaemia. Change in the proportion of patients with cured LH. All adverse events.
Chen et al[13]	Location: China Sample size: 210 Detection method of LH: visible and/or palpable LH determined by nurses and ultrasound examination	Age (years): 59±7 (IT), 60±9 (C) Male (%): 46.7 Number of T1DM/T2DM individuals: N/A Estimated diabetes duration (years): 14.4±5.8 (IT), 16.8±7.6 (C) Insulin treatment duration (years): 6.9±4.7 (IT), 7.1±5.4 (C)	IT: reducing insulin doses initially by 20%, instructing to rotate within injection sites, foregoing needle reuse, stopping injecting into the LH site and switching to 4 mm needles. C: standard care.	Change in TDD of insulin from baseline. Change in HbA1c levels from baseline. Hypoglycaemia. Change in the proportion of patients with cured LH. All adverse events.
Gentile et al[21]	Location: Italy Sample size: 318 Detection method of LH: inspection and palpation by healthcare professionals and ultrasound-based skin evaluations	Age (years): 61±10 (IT), 63±12 (C) Male (%): 44.0 Number of T1DM/T2DM individuals: 0/318 Estimated diabetes duration (years): 11.6±9.8 (IT), 11.3±5.7 (C) Insulin treatment duration (years): 6.5±9.3 (IT), 6.7±7.2 (C)	IT: reducing insulin doses initially by 20%, repeatedly instructing to rotate within injection sites, foregoing needle reuse and stopping injecting into the LH site. Change to 4 mm needles 6 months before randomisation. Insulin titration. C: reducing insulin doses initially by 20%, at the first session instructing to rotate within injection sites, foregoing needle reuse and stopping injecting into the LH site. Change to 4 mm needles 6 months before randomisation. Insulin titration.	Change in TDD of insulin from baseline. Change in HbA1c levels from baseline. Hypoglycaemia. All adverse events.

C, control group; HbA1c, haemoglobin A1c; IT, injection technique education group; LH, lipohypertrophy; N/A, not available; TDD, total daily dose; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

The data collecting form included information on the first author's name, year of publication, country, sample size, proportion of male participants, mean age of participants, number of participants with type 1 diabetes mellitus (T1DM)/type 2 diabetes mellitus (T2DM), estimated diabetes duration, mean duration of insulin treatment, intervention details, detection methods of LH and the outcome measures mentioned above. We asked the authors of the original papers for unpublished or additional data and obtained research data for ref 13 but not for ref 12.

Study risk of bias assessment

Two reviewers (MI and TA) independently assessed the risk of bias using the Risk of Bias 2 (RoB2) tool.[16] The effect of interest is the intention-to-treat effect, which is the effect assigned to the interventions at baseline, regardless of whether or not the intervention was received as intended. Disagreements between the two reviewers were discussed, and if this was not possible, a third reviewer (YTs or KA) became an arbiter.

Effect measures

We pooled the relative risk ratios (RR) and 95% CIs for the following binary variables: hypoglycaemia and proportion of patients with cured LH. We pooled the mean differences (MD) and 95% CIs for the following continuous variables: HbA1c and TDD of insulin.

We extracted the data on an intention-to-treat basis for all dichotomous data whenever possible. For continuous
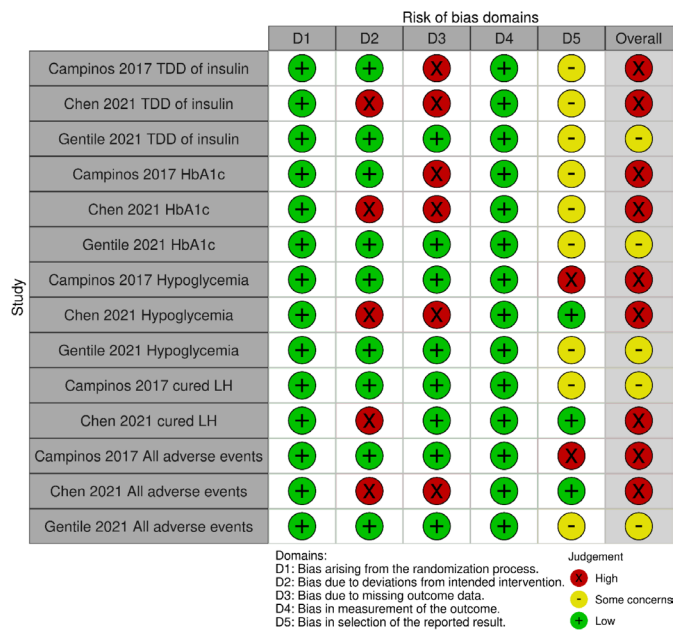
Figure 2 Risk of bias evaluation for each outcome. The risk of bias was assessed using the Cochrane risk of bias tool for randomised trials. LH, lipohypertrophy; TDD, total daily dose.

data, we did not impute missing data based on the recommendation of the Cochrane Handbook.[17] We performed a meta-analysis of the data available in the original study.

When the original studies reported only SEs or p values, we used Altman's method to calculate the SD.[18] When these values were not available after enquiring the authors, we calculated the SDs using CIs and t-values based on the methods in the Cochrane Handbook[17] or validated methods.[18] We analysed the validity of these methods using sensitivity analysis.

Statistical analyses

We used Review Manager software (RevMan V.5.4; The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) to conduct a meta-analysis using the DerSimonian and Laird random-effects method. We assessed statistical heterogeneity by visual inspection of the forest plots and calculation of I^2 statistic (I^2 values of 0%–40%: might not be important; 30%–60%: may represent moderate heterogeneity; 50%–90%: may represent substantial heterogeneity; 75%–100%: considerable heterogeneity). For the I^2 statistic, we performed the Cochrane χ^2 test (Q test) and considered it statistically significant if the p value was <0.10.

Certainty assessment

Based on the Cochrane Handbook,[17] we created a summary of findings (SoF) table for the results of changes in the insulin TDD, changes in HbA1c levels and the prevalence of hypoglycaemia. A SoF table contained important information on the relative and absolute effect sizes of the interventions investigated, the amount of available evidence and the certainty of available evidence.[17]

We assessed the quality of evidence for each outcome based on the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) method.[19]

Table 2 Summary of findings comparing indicated outcomes between injection technique education and standard care

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of evidence (GRADE)
	Assumed risk—C	Corresponding risk—IT			
Change in TDD of insulin	Mean change in the TDD of insulin in the C group was −3.12 to −0.9.	Mean change in the TDD of insulin in the IT group was 6.26 lower (9.42 lower to 3.10 lower).		637 (3)	Low†‡
Change in HbA1c level	Mean change in HbA1c level in the C group was −0.55 to 0.1.	Mean change in HbA1c level in the IT group was 0.59 lower (1.71 lower to 0.54 higher).		637 (3)	Very low†‡§
Prevalence of hypoglycaemia	162/319 (50.8%)	21/318 (6.60%)	RR 0.44 (0.06 to 3.13)	637 (3)	Very low†§¶

Patient or population: patients with type 1 diabetes or type 2 diabetes who use insulin and have LH.
Setting: outpatient.
Intervention: injection technique education.
Comparison: standard care.
GRADE Working Group grades of evidence: High quality: we are very confident that the true effect lies close to that of the estimate of the effect. Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.
*Corresponding risk (and 95% CI) are based on assumed risks in the control group and relative risks (and 95% CI) of the intervention.
†Due to serious risk of bias.
‡Due to serious imprecision. The sample size did not meet the optimal size criterion.
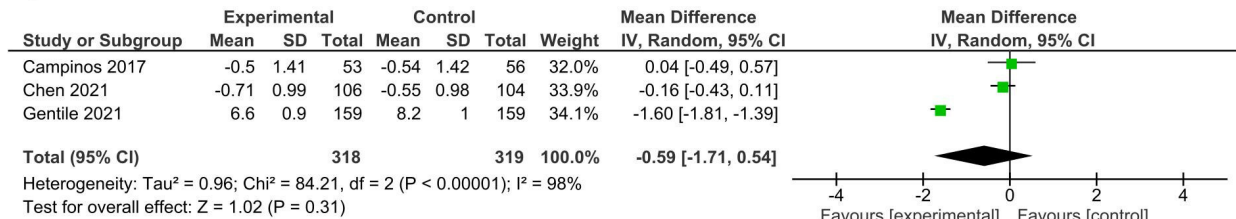§Due to serious inconsistency.
¶Due to very serious imprecision. The sample size did not meet the optimal size criterion, and the 95% CI was wide.
C, control; GRADE, Grading of Recommendations, Assessment, Development and Evaluation; HbA1c, haemoglobin A1c; IT, injection technique; LH, lipohypertrophy; RR, risk ratio; TDD, total daily dose.
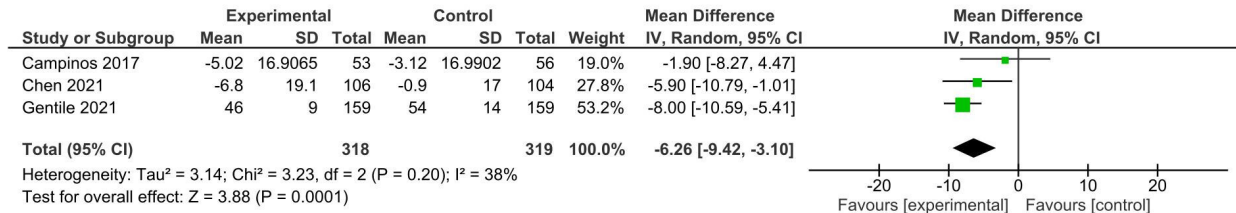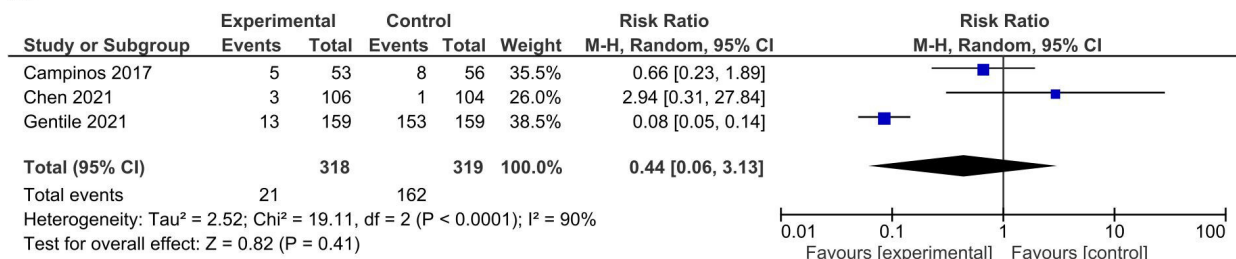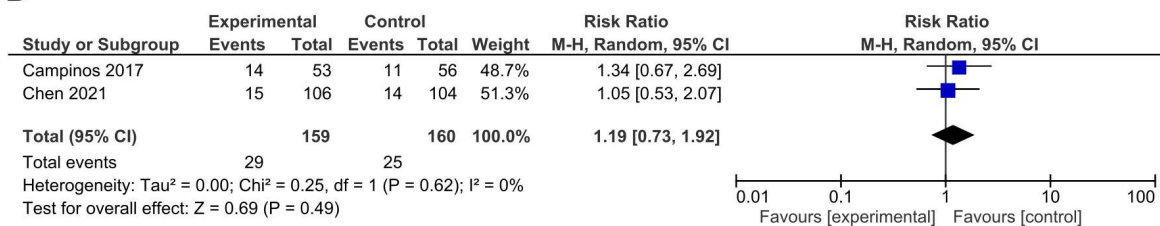
Figure 3 Forest plots of primary and secondary outcomes. (A) Change in total daily dose of insulin. (B) Change in HbA1c levels. (C) Prevalence of hypoglycaemia. (D) Change in the proportion of patients with cured lipohypertrophy (LH).

GRADE specifies four categories, namely high, moderate, low and very low, which are applied to accumulating evidence. Evidence from randomised trials starts with high certainty of evidence and can be downgraded by five domains: risk of bias, imprecision, inconsistency, indirectness and publication bias.

Difference between a protocol and a review

The duration of hypoglycaemia was defined as the follow-up period, but as it was reported in terms of the number of patients who had hypoglycaemia, the duration was defined as the longest follow-up after 3 months. We could not summarise all adverse events because there were few reports other than hypoglycaemia. To clarify the influence of effect modifiers on the results, subgroup analyses of the primary outcome were planned to be evaluated with the following factors when sufficient data were available: age (<65 years vs ≥65 years), baseline HbA1c level of <8% vs ≥8%,[20] sex and IT protocol with or without initial insulin-level reduction.

We also planned to conduct the following sensitivity analyses on the primary outcomes to assess whether the results of the review were robust to the decisions made during the review process: exclusion of studies with imputed statistics, and exclusion of studies with an overall high risk of bias. We could not perform a predetermined subgroup analysis and sensitivity analysis because of insufficient data.

We planned to assess the possibility of publication bias by visually inspecting the funnel plots and testing the Egger's test. If there were fewer than 10 trials or trials with similar sample sizes, then we decided not to perform the test. We could not perform the Egger's test

for reporting bias detection because there were fewer than 10 trials.

Patient and public involvement

As this was a systematic review, patients or the public were not involved in our research.

RESULTS
Study selection

We performed the search in November 2021 and found 580 records; after duplicates were removed, 550 records were screened for titles and abstracts. Nine full-text records were assessed for eligibility. Six studies were excluded, and the reasons were as follows: five for including the wrong population and one for using the wrong design. Details of the excluded studies are shown in the online supplemental table S3. Finally, we included three RCTs that met the eligibility criteria (figure 1).[12 13 21]

Study characteristics

Table 1 presents the characteristics of the three included studies conducted in France, China and Italy. In the French study, the number of individuals with T1DM/T2DM was 66/57, and in the Italian study, it was 0/318. In the Chinese study, there were fewer than seven patients with T1DM, but the exact number of patients with T1DM/T2DM could not be obtained despite inquiries. In the French study, all participants received information about optimal IT and LH at baseline for ethical reasons. In the Italian study, the proportion of cured LH was not reported.

Risk of bias in the studies

Figure 2 shows the RoB2 result: in two of three RCTs,[12 13] domain 2 (bias due to deviations from the intended intervention) and/or domain 3 (bias due to missing outcome data) were at high risk, and the overall risk of bias was high.

Outcome and certainty of evidence

Table 2 shows a summary of these findings. Figure 3 shows a forest plot. Compared with standard care, IT slightly increased the change in TDD of insulin (three studies, 637 participants: MD −6.26; 95% CI −9.42 to −3.10; p<0.001; I^2=38%; low certainty of evidence). The certainty of evidence was low because of serious risk of bias and imprecision. Compared with standard care, IT may increase little to no effect on the change in HbA1c levels but the evidence is very uncertain (three studies, 637 participants: MD −0.59; 95% CI −1.71 to 0.54; p=0.31; I^2=98%; very low certainty of evidence). The certainty of evidence was very low because of serious risk of bias, imprecision and inconsistency.

The evidence is very uncertain about the effect of insulin IT on the prevalence of hypoglycaemia (three studies, 637 participants: RR 0.44; 95% CI 0.06 to 3.13; p=0.41; I^2=90%; very low certainty of evidence). The very low certainty of evidence was due to the serious risk of

bias and inconsistency and the very serious imprecision. The evidence is very uncertain about the prevalence of cured LH compared with the control group (two studies, 319 participants: RR 1.19; 95% CI 0.73 to 1.92; p=0.49; I^2=0%; very low certainty of evidence). The very low certainty of evidence was due to the serious risk of bias and very serious imprecision.

DISCUSSION

The present study showed that IT may result in a slight reduction in the TDD of insulin. The evidence is very uncertain about the effect of insulin IT on the change in HbA1c levels, the prevalence of hypoglycaemia and the prevalence of cured LH compared with those in the control group. To the best of our knowledge, this is the first systematic review and meta-analysis to study the effects of insulin IT in comparison with standard care for patients with diabetes with LH.

The results of the present study were partly consistent with those of previous observational studies, which found that IT was associated with changes in TDD of insulin and HbA1c levels.[9 10] These previous observational studies reported that IT decreased the TDD of insulin and HbA1c levels in patients with diabetes on insulin injection. Our meta-analysis of randomised trials showed similar results of TDD of insulin. Meanwhile, the results of the present study did not show a decrease in HbA1c levels, but this might be due to the fact that the three studies included were initially conducted with up to 20% reduction in TDD of insulin to prevent hypoglycaemia.

Excessive exogenous insulin can be harmful, and it is important to reduce the TDD of insulin to prevent adverse events. Excessive exogenous insulin administration has been reported to be associated with adverse events such as hypoglycaemia, weight gain and increased cardiovascular events and mortality.[22 23] A meta-analysis in patients with type 1 diabetes integrated aerobic-only intervention studies in adults, and multiple types of exercise interventions, including aerobic and anaerobic, in 12–18 year-olds. The results showed a reduction of 0.21 U/kg in TDD of insulin.[24] The present study showed a decrease in insulin TDD of 6.26 U/day with improved pharmacokinetics/pharmacodynamics by IT education. Therefore, although the effects obtained by exercise interventions, which have different mechanism, showed greater results, IT education may be effective in avoiding excessive doses of insulin.

The certainty of evidence in the present study was low or very low. In one included study,[13] a portion of the control group was shifted to the ideal injection method, which contributed to the effect of high risk of bias due to deviation from the intended intervention. In the other two studies, some of the control group was shifted to the ideal injection method.[12 21] Despite the fact that some of the control group shifted to the ideal injection method, the present study showed a slight reduction in the TDD of insulin, which underestimates the effect. In fact, the

effect may be even greater. In two of three studies,[12 13] the bias due to missing outcome data for the continuous variable outcome was high because the missing value was greater than 5%. The bias due to missing outcome data for the binary variable outcome was low or high for the frequency of outcome and number of missing outcomes. The registration of the prevalence of hypoglycaemia in ClinicalTrials.gov mentions only a timeframe of 6 months, but because the prevalence of hypoglycaemia was counted at 3 and 6 months, we considered the bias in the selection of the ref [12] as high. The other reason for lowering the GRADE is imprecision, because only three studies were included, and the sample size was small. In the future, more studies with sufficient sample sizes are needed.

The strengths of this study are that we conducted a comprehensive search and summarised the evidence for the effects of IT, used a prospective registered protocol, followed the Cochrane Handbook and GRADE, selected a rigorous methodology and adhered to reporting guidelines.

However, this study had several limitations. First, as described above, we could not have enough data to conduct subgroup analyses and assess publication bias. It was not plausible for publication bias to affect our findings because our comprehensive search did not show any ongoing or unpublished studies. Second, the generalisability of our findings is limited. For example, the included studies tended to recruit middle-aged, obese and patients with type 2 diabetes, and measured the outcomes at 6 months. However, a cross-over study limited to type 1 diabetes individuals has shown that injections administered at sites away from the LH improved insulin absorption and reduced glycaemic variability compared with injections administered at the LH.[8] Previous studies have also shown the efficacy of optimised IT on TDD of insulin, although baseline characteristics varied, suggesting that it may be effective in the aforementioned populations.[9 10] Further studies evaluating different populations and long-term outcomes are required. Third, we could not perform a subgroup analysis of types of diabetes mellitus (DM) which was requested during peer review due to the limited data. The prevalence of LH was higher in type 2 diabetes than in type 1 diabetes, thus the types of DM may be an effect modifier of IT.[4] Future studies that use individual participant data can assess the effect modification. Fourth, we could not evaluate the effects beyond 6 months in this study. The two studies [21 25]) had a 12-month follow-up duration, and although the latter study[25] did not meet the eligibility criteria of this study, their findings suggest that repeating the education on IT has lasting effects.[21 25]

CONCLUSION

The present meta-analysis suggests that providing education on IT to patients with diabetes with LH may slightly reduce the TDD of insulin. Clinicians may consider providing IT to patients with diabetes with LH, but they also need to understand the uncertainty of the evidence. In the future, we hope that RCTs with less bias, especially for the deviation of the intended protocol and with a rigorous protocol, will be conducted to accurately evaluate the effects.

ORCID iDs
Masahiro Ichikawa http://orcid.org/0000-0002-6594-5342
Yasuo Terauchi http://orcid.org/0000-0002-8872-3697

REFERENCES

1 Federation ID. IDF diabetes atlas. 9th ed. Available: http://www.diabetesatlas.org/ [Accessed 11 Jun 2021].
2 Brown A, Guess N, Dornhorst A, *et al*. Insulin-associated weight gain in obese type 2 diabetes mellitus patients: what can be done? *Diabetes Obes Metab* 2017;19:1655–68.
3 Basu S, Yudkin JS, Kehlenbrink S, *et al*. Estimation of global insulin use for type 2 diabetes, 2018-30: a microsimulation analysis. *Lancet Diabetes Endocrinol* 2019;7:25–33.
4 Deng N, Zhang X, Zhao F, *et al*. Prevalence of lipohypertrophy in insulin-treated diabetes patients: a systematic review and meta-analysis. *J Diabetes Investig* 2017;9:536–43.
5 Frid AH, Kreugel G, Grassi G, *et al*. New insulin delivery recommendations. *Mayo Clin Proc* 2016;91:1231–55.
6 Gentile S, Guarino G, Corte TD, *et al*. Insulin-induced skin lipohypertrophy in type 2 diabetes: a multicenter regional survey in Southern Italy. *Diabetes Ther* 2020;11:2001–17.
7 Blanco M, Hernández MT, Strauss KW, *et al*. Prevalence and risk factors of lipohypertrophy in insulin-injecting patients with diabetes. *Diabetes Metab* 2013;39:445–53.
8 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;39:1486–92.

9 Grassi G, Scuntero P, Trepiccioni R, *et al*. Optimizing insulin injection technique and its effect on blood glucose control. *J Clin Transl Endocrinol* 2014;1:145–50.

10 Smith M, Clapham L, Strauss K. UK lipohypertrophy interventional study. *Diabetes Res Clin Pract* 2017;126:248–53.

11 Misnikova IV, Gubkina VA, Lakeeva TS, *et al*. A randomized controlled trial to assess the impact of proper insulin injection technique training on glycemic control. *Diabetes Ther* 2017;8:1309–18.

12 Campinos C, Le Floch J-P, Petit C, *et al*. An effective intervention for diabetic lipohypertrophy: results of a randomized, controlled, prospective multicenter study in France. *Diabetes Technol Ther* 2017;19:623–32.

13 Chen L, Xing Q, Li J, *et al*. Injection technique education in patients with diabetes injecting insulin into areas of lipohypertrophy: a randomized controlled trial. *Diabetes Ther* 2021;12:813–26.

14 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;91:1224–30.

15 Page MJ, McKenzie JE, Bossuyt PM, *et al*. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71.

16 Sterne JAC, Savović J, Page MJ, *et al*. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;366:l4898.

17 Higgins JPT. *Cochrane Handbook for systematic reviews of interventions version 6.0 Cochrane*, 2019. http://www.training. cochrane.org/handbook

18 Furukawa TA, Barbui C, Cipriani A, *et al*. Imputing missing standard deviations in meta-analyses can provide accurate results. *J Clin Epidemiol* 2006;59:7–10.

19 Guyatt G, Oxman AD, Akl EA, *et al*. Grade guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol* 2011;64:383–94.

20 Duke S-AS, Colagiuri S, Colagiuri R. Individual patient education for people with type 2 diabetes mellitus. *Cochrane Database Syst Rev* 2009:CD005268.

21 Gentile S, Guarino G, Della Corte T, *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;12:1379–98.

22 McCall AL. Insulin therapy and hypoglycemia. *Endocrinol Metab Clin North Am* 2012;41:57–87.

23 Herman ME, O'Keefe JH, Bell DSH, *et al*. Insulin therapy increases cardiovascular risk in type 2 diabetes. *Prog Cardiovasc Dis* 2017;60:422–34.

24 Yardley JE, Hay J, Abou-Setta AM, *et al*. A systematic review and meta-analysis of exercise interventions in adults with type 1 diabetes. *Diabetes Res Clin Pract* 2014;106:393–400.

25 Gentile S, Guarino G, Della Corte T, *et al*. The durability of an intensive, structured Education-Based rehabilitation protocol for best insulin injection practice: the ISTERP-2 study. *Diabetes Ther* 2021;12:2557–69.