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Efficacy of injection technique education in diabetes with lipohypertrophy: a systematic review and meta-analysis protocol

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Summary: 1.IntroductionMany patients with diabetic mellitus who use insulin develop changes in the subcutaneous adipose tissue at the injection site. These lesions are called lipohypertrophy (LH). The prevalence of LH was reported to be 30-50% or more (1). In a randomized crossover study, injections into sites of LH showed blunted insulin absorption and increased variability compared to injections into normal adipose tissues (2).Since sites of LH reduce the absorption of insulin, patients with LH often use higher total daily doses (TDD) of insulin and have worsened glucose control and higher hyperglycemic hemoglobin (HbA1c) levels (3-5). LH may increase the risk of adverse clinical outcomes and the cost of healthcare.Recently, the effect of injection technique (IT) education to avoid the injection into LH and improve glycemic control on patients with LH has been reported (1, 6).IT education includes stopping injections into LH, stopping needle reuse, and rotating injection sites. However, no meta-analysis has been performed. Thus, to assess the impact of IT education on clinical and metabolic parameters in adults with LH, we will summarize current evidence.2.Research questionP: Patients with type 1 diabetes or type 2 diabetes who are injecting insulin and have LH.I: Injection technique educationC: standard careO: change in TDD3.Method3.1 ProtocolWe used a systematic review protocol template(dx.doi.org/10.17504/protocols.io.biqrkdv6). We followed the Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 for preparing this protocol(7). We will publish this protocol in protocols.io (https://www.protocols.io/).3.2 Inclusion criteria of the articles for the review3.2.1 Type of studiesWe will include individual, cluster, and cross-over randomized trials that assess the

injection technique education in patients with type 1 or type 2 diabetes who are injecting insulin and have LH. We will not apply language or country restrictions. We will include all papers including published, unpublished articles, abstract of conference and letter. We will exclude observational studies and non randomized controlled trials. We will not exclude studies based on the observation period or publication year.

3.2.2 Study participants

We will include patients with type 1 or type 2 diabetes who have been on insulin injections for at least 1 year, with LH, 18 years of age or older, any gender, no HbA1c restriction, and no education about LH within the past 6 months. The diagnosis of LH were made by a physician or nurse when it is clinically visible, palpable, or visible on ultrasound (8). We will accept any number of insulin injections per day, or size of needle or length for insulin injections. We will exclude pregnant women, patients who wish to become pregnant, lactating women and patients taking medications that may cause LH (anti-retroviral or corticosteroid therapy).

3.2.3 Intervention

IT education: Stop injecting into the LH site, stop reusing needles, and rotate injection sites. We will also accept other definitions of IT education. Any education period is acceptable.

3.2.4 Control

Standard care (no intervention, usual care).

3.3 Type of outcomes

3.3.1 Primary outcomes

1. Change in total daily doses of insulin

Definition: Change in total daily doses of insulin from baseline

Period: Time frame is the longest follow-up period after 3 months
2. Change in HbA1c

Definition: Change in HbA1c from baseline

Period: Time frame is the longest follow-up period after 3 months
3. Hypoglycemia

Definition: Hypoglycaemia was defined as the occurrence of one or more symptoms of hypoglycaemia (such as palpitations, tiredness, sweating, strong hunger, dizziness and tremor) and a confirmed blood glucose meter reading of ≤ 60 mg/dL (4). We will also accept hypoglycemia as the original investigators defined.

Period: during follow up period

3.3.2 Secondary outcomes

1. Change in proportion of patients with cured LH

Definition: as original investigators defined

Period: Time frame is the longest follow-up period after 3 months
2. All adverse events

Definition: definition of adverse events are set by original authors.

Period: during follow up period

3.4 Search method

3.4.1 Electronic search

We will search the following databases: 1. the Cochrane Central Register of Controlled Trials (CENTRAL); 2. MEDLINE via PubMed; 3. EMBASE via ProQuest Dialog; See Appendix 1, 2, and 3 for the search strategies.

3.4.2 Other resources

We will also search the following databases for ongoing or unpublished trials: 1. the World Health Organization International Clinical Trials Platform Search Portal (ICTRP); 2. ClinicalTrials.gov; See Appendix 4, 5 for the search strategies. We will check the reference lists of studies, including international guidelines as well as the reference lists of eligible studies and articles citing eligible studies. We will ask the authors of original studies for unpublished or additional data.

3.5 Data collection and analysis

3.5.1 Selection of the studies

Two independent reviewers will screen titles and abstracts, followed by the assessment of the eligibility based on the full texts. We will contact original authors if relevant data is missing. Disagreements between the two reviewers will be resolved by discussion, and if this fails, a third reviewer will act as an arbiter.

3.5.2 Data extraction and management

Two reviewers will perform independent data extraction of the included studies using standardized data collection form. The form will include the information on the first author's name, year of study publication, country, sample size, proportion of male participants, mean age of participants, the number of participants with type 1 diabetes mellitus/type 2 diabetes mellitus, estimated diabetic duration, mean duration of insulin treatment, intervention details, detection methods of LH and the outcome measures above. Any disagreements will be resolved by discussion, and if this fails, a third reviewer will act as an arbiter.

3.6 Assessment of risk of bias in included studies

Two reviewers will evaluate the risk of bias independently using the Risk of Bias 2 tool (9). The effect of interest is the intention-to-treat effect; the effect of assignment to the interventions at

baseline, regardless of whether the interventions are received as intended. Disagreements between the two reviewers will be discussed, and if this fails, a third reviewer will be acting as an arbiter, if necessary.

3.7 Measures of treatment effects We will pool the relative risk ratios and the 95% confidence intervals (CIs) for the following binary variables: Hypoglycemia, proportion of patients with cured LH and all adverse events. We will pool the mean differences and the 95% CIs for the following continuous variables: HbA1c, total daily doses of insulin. We will summarize adverse events based on the definition by the original article, but we will not perform meta-analysis.

3.8 Unit of analysis issues Clustering at the level of the enrolled units in cluster randomised studies. In dealing with cluster-RCTs, for dichotomous data, we will apply the design effect and calculate effective sample size and number of events using the intracluster correlation coefficient (ICC) among each unit and the average cluster size, as described in Chapter 16.3.5 of the Cochrane Handbook (10). If the ICC has not been reported, we will use the ICC of a similar study as a substitute. For continuous data, only the sample size will be reduced; means and standard deviation will remain unchanged (10).

Randomised cross-over studies We will consider only data from the first period.

Multiple comparisons All intervention groups that are relevant to this review will be included.

3.9 Handling of missing data We will ask not-presented data to the original authors.

3.9.1 Missing outcomes We will perform the intention-to-treat (ITT) analysis for all dichotomous data as much as possible. For continuous data, we will not impute missing data based on the recommendation by Cochrane handbook (10). We will perform meta-analysis about the available data in the original study.

3.9.2 Missing statistics When original studies only report standard error or p-value, we will calculate the standard deviation based on the method by Altman (11). If we could not obtain these values by contacting authors, standard deviation will be calculated by confidence interval and t-value based on the method by Cochrane handbook (10), or validated method (11). Validity of these methods will be analyzed by sensitivity analysis.

3.10 Assessment of heterogeneity We will evaluate the statistical heterogeneity by visual inspection of the forest plots and calculating the I^2 statistic (I^2 values of 0% to 40%: might not be important; 30% to 60%: may represent moderate heterogeneity; 50% to 90%: may represent substantial heterogeneity; 75% to 100%: considerable heterogeneity). When there is substantial heterogeneity ($I^2 > 50\%$), we will assess the reason of the heterogeneity. Cochrane Chi² test (Q-test) will be performed for I^2 statistic, and P value less than 0.10 will be defined as statistically significant.

3.11 Assessment of reporting bias We will search the clinical trial registry system (ClinicalTrials.gov and ICTRP) and will perform extensive literature search for unpublished trials. We will assess the potential publication bias by visual inspection of the funnel plot. Egger's test will be performed as well. We will not conduct the test when we find less than 10 trials or trials which have similar sample size. We will assess the potential publication bias by visual inspection of the funnel plot.

3.12 Meta-analysis Meta-analysis will be performed using Review Manager software (RevMan 5.4). We will use a random-effects model.

3.13 Subgroup analysis To elucidate the influence of effect modifiers on results, we will evaluate the subgroup analyses of the primary outcomes on the following factors when sufficient data are available: 1. age 2. baseline HbA1c 3. gender 4. IT education protocols with versus without initial insulin reduction.

3.14 Sensitivity analysis We will undertake the following sensitivity analyses for the primary outcomes to assess whether the results of the review are robust to the decisions made during the review process: 1. Exclusion of studies using imputed statistics. 2. Exclusion of studies with high overall risk of bias. 4. Summary of findings table. Summary of findings table will be made for the following outcome based on the Cochrane handbook (10). We will include grading to evaluate the quality of evidence based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE)

approach for each Summary of findings table (13).1. Change in total daily doses of insulin2. Change in HbA1c3. Hypoglycemia5. Conflict of InterestThe authors declare no conflicts of interests.

Appendix 1: CENTRAL search strategy#1[mh Amyloidosis]#2 lipohypertrophy:ti,ab#3 "insulin-derived amyloidosis":ti,ab #4lipos:ti,ab#5 "subcutaneous induration":ti,ab#6"subcutaneous nodules":ti,ab#7 #1 OR #2 OR #3 OR #4 OR #5 OR #6#8 [mh "Injections, Subcutaneous"]#9 [mh "Patient Education as Topic"]#10injection*:ti,ab#11 education*:ti,ab#12 (reus*:ti,ab AND needle*:ti,ab)#13 #8 OR #9 OR #10 OR #11 OR #12#14 #7 AND #13Appendix 2: MEDLINE (via PubMed) search strategy#1 "Amyloidosis"[Mesh]#2 "lipohypertrophy"[tiab]#3 "insulin-derived amyloidosis"[tiab]#4 "lipos"[tiab]#5 "subcutaneous induration"[tiab]#6 "subcutaneous nodules"[tiab]#7 #1 OR #2 OR #3 OR #4 OR #5 OR #6#8 "Injections, Subcutaneous"[Mesh]#9 "Patient Education as Topic"[Mesh]#10 injection*[tiab] #11 education*[tiab] #12 reus*[tiab] AND needle*[tiab]#13 #8 OR #9 OR #10 OR #11 OR #12#14 #7 AND #13#15 randomized controlled trial[pt]#16 controlled clinical trial[pt]#17 randomized[tiab]#18 placebo[tiab]#19 drug therapy[sh]#20 randomly[tiab]#21 trial[tiab]#22 groups[tiab]#23 #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22#24 animals[mh] NOT humans[mh]#25 #23 NOT #24#26 #14 AND #25Appendix 3: EMBASE (via ProQuest Dialog) search strategy#1 emb(amyloidosis) OR ti(lipohypertrophy) OR ab(lipohypertrophy) OR ti(insulin-derived amyloidosis) OR ab(insulin-derived amyloidosis) OR ti(lipos) OR ab(lipos) OR ti(subcutaneous induration) OR ab(subcutaneous induration) OR ti(subcutaneous nodules) OR ab(subcutaneous nodules) #2 exact(subcutaneous drug administration) OR exact(patient education) OR ti(injection*) OR ab(injection*) OR ti(education*) OR ab(education*) OR (ti(reus*) OR ab(reus*)) AND (ti(needle*) OR ab(needle*)) #3 (ab(random*) OR ti(random*)) OR (ab(clinical NEAR/1 trial*) OR ti(clinical NEAR/1 trial*)) OR (EMB.EXACT("health care quality"))#4 #1 AND #2 AND #3Appendix 4: ICTRP search strategyParticipant: lipohypertrophy OR insulin-derived amyloidosis OR subcutaneous induration OR subcutaneous nodulesIntervention: injection OR education OR (reus AND needle)Appendix 5: ClinicalTrials.gov search strategyCondition or disease: lipohypertrophy OR insulin-derived amyloidosis OR subcutaneous induration OR subcutaneous nodulesIntervention: injection OR education OR (reus AND needle)References1.Chen L, Xing Q, Li J, Zhou J, Yuan Y, Wan Y, et al. Injection Technique Education in Patients with Diabetes Injecting Insulin into Areas of Lipohypertrophy: A Randomized Controlled Trial. *Diabetes Ther.* 2021.2.Famulla S, Hövelmann U, Fischer A, Coester H-V, Hermanski L, Kaltheuner M, 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):1486-92.3.Frid AH, Hirsch LJ, Menchior AR, Morel DR, Strauss KW. Worldwide Injection Technique Questionnaire Study: Injecting Complications and the Role of the Professional. *Mayo Clinic proceedings.* 2016;91(9):1224-30.4.Blanco M, Hernández MT, Strauss KW, Amaya M. Prevalence and risk factors of lipohypertrophy in insulin-injecting patients with diabetes. *Diabetes Metab.* 2013;39(5):445-53.5.Ji L, Sun Z, Li Q, Qin G, Wei Z, Liu J, et al. Lipohypertrophy in China: Prevalence, Risk Factors, Insulin Consumption, and Clinical Impact. *Diabetes Technol Ther.* 2017;19(1):61-7.6.Campinos C, Le Floch JP, Petit C, Penfornis A, Winiszewski P, Bordier L, et al. An Effective Intervention for Diabetic Lipohypertrophy: Results of a Randomized, Controlled, Prospective Multicenter Study in France. *Diabetes Technol Ther.* 2017;19(11):623-32.7. Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ.* 2015;349(jan02 1):g7647-g7647. doi:10.1136/bmj.g76478.8.Deg N,Zhang X, Zhao F, Wang Y, He H. Prevalence of lipohypertrophy in insulin-treated diabetes patients: A systematic review and meta-

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