



Version 3

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# Efficacy of injection technique education in diabetes with lipohypertrophy: a systematic review and meta-analysis protocol V.3

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1 Works for me [dx.doi.org/10.17504/protocols.io.btiinkce](https://dx.doi.org/10.17504/protocols.io.btiinkce)

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SUBMIT TO PLOS ONE

## ABSTRACT

### 1. Introduction

Many diabetic patients 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 glycemic 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, rotating injection site, and switching to 4 mm needles. 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 question

P: Patients with type 1 diabetes or type 2 diabetes who are injecting insulin and have LH.

I: Injection technique education

C: standard care

O: change in TDD

### 3. Method

#### 3.1 Protocol

We used a systematic review protocol template([dx.doi.org/10.17504/protocols.io.biqrkdv6](https://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 review

##### 3.2.1 Type of studies

We 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, nurse or investigators 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 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, rotate injection sites, and switch to 4 mm needles. We will also include other education that aimed to improve lipohypertrophy and 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  $\leq 60$  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 Chi<sup>2</sup> 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 (<65 vs  $\geq 65$  years old)
2. baseline HbA1c <8% vs  $\geq 8\%$  (12)
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 insulin
2. Change in HbA1c
3. Hypoglycemia

### 5. Conflict of Interest

The 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 #13

#### Appendix 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 #25

#### Appendix 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 #3

#### Appendix 4: ICTRP search strategy

Participant: lipohypertrophy OR insulin-derived amyloidosis OR subcutaneous induration OR subcutaneous nodules

Intervention: injection OR education OR (reus AND needle)

#### Appendix 5: ClinicalTrials.gov search strategy

Condition or disease: lipohypertrophy OR insulin-derived amyloidosis OR subcutaneous induration OR subcutaneous nodules

Intervention: injection OR education OR (reus AND needle)

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#### ATTACHMENTS

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#### KEYWORDS

lipohypertrophy, diabetes mellitus, injection technique education

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## ABSTRACT

## 1.Introduction

Many diabetic patients 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).

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## 2.Research question

P: Patients with type 1 diabetes or type 2 diabetes who are injecting insulin and have LH.

I: Injection technique education

C: standard care

O: change in TDD

## 3.Method

## 3.1 Protocol

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## 3.2.3 Intervention

IT education: Stop injecting into the LH site, stop reusing needles, rotate injection sites, and switch to 4 mm needles. We will also include other education that aimed to improve lipohypertrophy and 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  $\leq 60$  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

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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..

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Clustering at the level of the enrolled units in cluster randomised studies

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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).

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2. Change in HbA1c
3. Hypoglycemia

#### 5. Conflict of Interest

The authors declare no conflicts of interests.

#### Appendix 1: CENTRAL search strategy

```
#1[mh Amyloidosis]
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#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 #13
```

#### Appendix 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 #25

#### Appendix 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 #3

#### Appendix 4: ICTRP search strategy

Participant: lipohypertrophy OR insulin-derived amyloidosis OR subcutaneous induration OR subcutaneous nodules

Intervention: injection OR education OR (reus AND needle)

#### Appendix 5: ClinicalTrials.gov search strategy

Condition or disease: lipohypertrophy OR insulin-derived amyloidosis OR subcutaneous induration OR subcutaneous nodules

Intervention: injection OR education OR (reus AND needle)

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#### ATTACHMENTS

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