INPLASY PROTOCOL

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None.

The efficacy and safety profile of leptin replacement therapy for non-HAART associated lipodystrophic syndromes: A systematic review and meta-analysis

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Review question / Objective: **In people with lipodystrophic syndromes not due to highly active antiretroviral therapy (HAART), what is the estimated magnitude of the effect of leptin replacement therapy on: 1) Glycaemic profile: a) HbA1c b) Fasting glucose c) Fasting insulin; 2) Lipid profile: a) Total cholesterol b) Triglyceride c) HDL cholesterol d) LDL cholesterol; 3) Liver profile: a) AST b) ALT c) Albumin d) Liver fat percentage e) Liver volume; 4) Leptin level; and 5) Weight? In people with lipodystrophic syndromes not due to highly active antiretroviral therapy (HAART), how common are the following potential side effects related to leptin replacement therapy: 1) Hypoglycaemia; 2) Injection site reaction; 3) Nausea; 4) Abdominal pain; 5) Myalgia; 6) Severe adverse event reaction; 7) Discontinuation due to adverse events; and 8) Any other unexpected serious adverse reaction?**
Condition being studied: **Lipodystrophic syndromes not due to highly active anti-retroviral therapy (HAART).**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 15 January 2021 and was last updated on 15 January 2021 (registration number INPLASY202110047).

INTRODUCTION

Review question / Objective: **In people with lipodystrophic syndromes not due to highly active antiretroviral therapy (HAART), what is the estimated magnitude of the effect of leptin replacement therapy on: 1) Glycaemic profile: a) HbA1c b) Fasting glucose c) Fasting insulin; 2) Lipid profile: a) Total cholesterol b) Triglyceride c) HDL cholesterol d) LDL cholesterol; 3) Liver profile: a) AST b) ALT c) Albumin d) Liver fat percentage e) Liver volume; 4) Leptin level; and 5) Weight? In people with**

lipodystrophic syndromes not due to highly active antiretroviral therapy (HAART), how common are the following potential side effects related to leptin replacement therapy: 1) Hypoglycaemia; 2) Injection site reaction; 3) Nausea; 4) Abdominal pain; 5) Myalgia; 6) Severe adverse event reaction; 7) Discontinuation due to adverse events; and 8) Any other unexpected serious adverse reaction?

Rationale: The long term efficacy and safety profile of leptin replacement therapy for non-HAART associated lipodystrophic syndromes remains unclear.

Condition being studied: Lipodystrophic syndromes not due to highly active antiretroviral therapy (HAART).

METHODS

Search strategy: The systematic search for literature will be conducted and reported by an information retrieval specialist. Relevant studies will be identified by a computerised search of the Medline (OVID), http://www.ClinicalTrials.gov and Cochrane Central Register of Controlled Trials (CENTRAL) databases. The search strategy has been built around two key concepts related to the topic of interest. The first concept is related to leptin therapy and the second is related to people with lipodystrophy. An example of this search strategy has been piloted in Medline (OVID) and is shown in Appendix 1.

Participant or population: People with lipodystrophic syndromes (either partial or generalized, genetic or acquired). Lipodystrophic syndromes due to highly active antiretroviral therapy (HAART) will be excluded during screening.

Intervention: Leptin replacement therapy.

Comparator: Placebo or routine standard of care. If no comparator arm, comparison with baseline level.

Study designs to be included: RCT, non-RCT, or case series.

Eligibility criteria: Studies will be included if they fulfill all of the following criteria: 1) Included people with lipodystrophic syndromes not due to highly active antiretroviral therapy (HAART) and 2) Reported any of the efficacy or safety outcomes as described below.

Information sources: Electronic databases including Medline (OVID), http://www.ClinicalTrials.gov and Cochrane Central Register of Controlled Trials (CENTRAL).

Main outcome(s): A) Efficacy outcomes: 1) Glycaemic profile: a. HbA1c b. Fasting glucose c. Fasting insulin; 2) Lipid profile: a. Total cholesterol b. Triglyceride c. HDL cholesterol d. LDL cholesterol; 3) Liver profile: a. AST b. ALT c. Albumin d. Liver fat percentage e. Liver volume; 4) Leptin level; and 5) Weight; B) Safety outcomes: 1) Hypoglycemia; 2) Injection site reaction; 3) Nausea; 4) Abdominal pain; 5) Myalgia; 6) Severe adverse event reaction; 7) Discontinuation due to adverse events; and 8) Any potential unexpected serious adverse reaction. Duration of follow up: 3 months to 30 years.

Data management: Titles and/or abstracts of studies retrieved using the search strategy and those from additional sources will be screened independently by two review authors to identify studies that potentially meet the inclusion criteria outlined above. The full text of these potentially eligible studies will be retrieved and independently assessed for eligibility by two review team members. Any disagreement between them over the eligibility of particular studies will be resolved through discussion with a third reviewer. A standardised, pre-piloted form will be used to extract data from the included studies for assessment of study quality and evidence synthesis. Extracted information will include study setting; study population and participant demographics and baseline characteristics; details of the intervention and control conditions; study methodology; recruitment and study completion rates; outcomes and times of measurement; indicators of acceptability to

users; suggested mechanisms of intervention action; information for assessment of the risk of bias. Two review authors will extract data independently, discrepancies will be identified and resolved through discussion with a third author.

Quality assessment / Risk of bias analysis: The risk of bias for randomised controlled trials (RCTs) will be formally assessed using the Risk of Bias (RoB) 2 tool (Reference 1). The Newcastle-Ottawa Scale (NOS) will be used to assess the quality of the included non-RCTs or case series (Reference 2).

Strategy of data synthesis: For RCTs or non-RCTs, the pooled odds ratios (ORs) and 95% CIs will be calculated using the random-effects model (DerSimonian and Laird method) (Reference 3). For the continuous outcomes, the mean differences (MDs) and 95% confidence intervals (CIs) using an inverse-variance weighted model will be calculated. The absolute risk reduction (ARR)/absolute risk increase (ARI) and the associated number-needed-to-treat (NNT)/ number-needed-to-harm (NNH) will be calculated if the OR is statistically significant. For case series, the continuous outcomes, a generic inverse variance random effects model was used to estimate the magnitude of treatment effect. For the dichotomous outcomes, prevalence meta-analyses will be performed. Heterogeneity assessment will be performed using the I2 index and Chi2 test. Publication bias will be assessed using a funnel plot, eggers regression test and the rank correlation test. If either test reports statistical significance ($p < 0.05$), this will indicate asymmetry in the funnel plot. If the three investigations described above suggest publication bias, trim and fill (Duval & Tweedie, 2000) will be implemented. Calculations will be performed using RevMan version 5.4 and STATA version 16.1.

Subgroup analysis: The following subgroup analyses will be performed: 1) Normal versus low leptin levels at baseline; 2) Male versus female; 3) Follow up duration: a. Less than 6 months b. 6 months to 1 year c. Over 1 year; 4) Generalized versus partial lipodystrophy; 5) Different doses of leptin replacement therapy; 6) Duration of leptin replacement therapy; 7) Study type.

Sensibility analysis: The "one-study-removed" procedure will be used as a sensitivity analysis to determine whether the overall estimates between the interventions and outcomes are influenced by outlier studies.

Language: English only.

Country(ies) involved: Ireland.

Other relevant information: References: 1) Sterne JAC, Savovic J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:l4898. 2) Wells G SB, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. . The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2013. 3) DerSimonian R, Laird N. Meta-analysis in clinical trials. Controlled clinical trials. 1986;7(3):177-188. Appendix 1. Search strategy in Medline (OVID). 1) exp Leptin/ 2) (leptin* or myalept* or metreleptin or mettreleptin or r-metHuLeptin or N-Methionylleptin).ti,ab,kw. 3) or/1-2 4) lipodystroph*.ti,ab,kw. 5) (loss adj2 ("adipose tissue" or "fat tissue")). ti,ab,kw. 6) (absence adj2 ("adipose tissue" or "fat tissue")). ti,ab,kw. 7) or/4-6. 8) 3 and 7

Keywords: Lipodystrophy; lipodystrophic syndromes; leptin; metreleptin.

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