INPLASY PROTOCOL

To cite: Fan et al. Efficacy and safety of incretin-based therapies in patients with nonalcoholic fatty liver disease: a protocol for a systematic review and meta-analysis. Inplasy protocol 202050045. doi: 10.37766/inplasy2020.5.0045

Received: 11 May 2020

Published: 11 May 2020

**Corresponding author:**
**Pei-min Feng**

**zyydxxhk@163.com**

**Author Affiliation:**
**Hospital of Chengdu University of TCM**

**Support:** **NSFC (no: 81273630)**

**Review Stage at time of this submission:** **Preliminary searches.**

**Conflicts of interest:**
**The authors have no conflicts of interest to disclose.**

# Efficacy and safety of incretin-based therapies in patients with nonalcoholic fatty liver disease: a protocol for a systematic review and meta-analysis

Fan, SM[1]; Shi, XY[2]; Fan, YP[3]; Yang, LL[4]; Yao, J[5]; Feng, PM[6].

**Review question / Objective:** **The effect of incretin-based therapies on liver histology, liver fat content, liver enzymes and adverse events in patients with NAFLD.**
**Condition being studied:** **NAFLD is seriously affecting the general health due to its liver-related consequences (liver cirrhosis and hepatocellular carcinoma) and its great risk for extra-hepatic chronic complications (T2DM, MS and cardiovascular disease). The role of incretin-based therapies as a potential treatment for NAFLD has attracted much attention. Numerous studies have demonstrated the improvement effect of incretin-based therapies on liver histology, intrahepatic lipid and liver enzymes. However, Negative studies have been also reported in some clinical trials. The conclusion is still controversial.**

**INPLASY registration number:** This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 11 May 2020 and was last updated on 11 May 2020 (registration number INPLASY202050045).

## INTRODUCTION

**Review question / Objective:** **The effect of incretin-based therapies on liver histology, liver fat content, liver enzymes and adverse events in patients with NAFLD.**

**Rationale:** **New drugs are urgently needed for the treatment of NAFLD. The purpose of this meta-analysis is to assess the efficacy of incretin-based therapies in patients with NAFLD.**

**Condition being studied:** **NAFLD is seriously affecting the general health due to its liver-related consequences (liver cirrhosis and hepatocellular carcinoma) and its great risk for extra-hepatic chronic**

complications (T2DM, MS and cardiovascular disease). The role of incretin-based therapies as a potential treatment for NAFLD has attracted much attention. Numerous studies have demonstrated the improvement effect of incretin-based therapies on liver histology, intrahepatic lipid and liver enzymes. However, Negative studies have been also reported in some clinical trials. The conclusion is still controversial.

## METHODS

**Search strategy:** Two reviewers will independently search English language publications on PubMed, Embase, Cochrane Library and Web of Science databases from inception to July 2020. According to the PICOS principle, The main key search words will be: "exenatide" OR "liraglutide" OR "albiglutide" OR "lixisenatide" OR "dulaglutide" OR "glucagon-like peptide 1" OR "sitagliptin" OR "vildagliptin" OR "saxagliptin" OR "alogliptin" OR "linagliptin" OR "gemigliptin" OR "teneligliptin" OR "dipeptidyl peptidase-4 inhibitor" AND "nonalcoholic fatty liver disease" OR "NAFLD" OR "nonalcoholic fatty liver*" OR "nonalcoholic steatohepatiti*" OR "NASH" OR "fatty liver*". The reference lists of reviewed articles will be manually searched for additional relevant studies and the ClinicalTrial.gov registry will also be searched for unpublished trials. When incomplete information is available, attempts will be made to contact the study investigators for additional information. A third reviewer will be involved in a discussion for any disagreements.

**Participant or population:** Adult (age ≥ 18 year) patients with a definitive diagnosis of NAFLD or NASH by histologic or imaging evidence (ultrasound, computer tomography or magnetic resonance imaging.

**Intervention:** GLP-1RAs (liraglutide, exenatide, albiglutide, lixisenatide and dulaglutide) or DPP-IVi (sitagliptin, vildagliptin, saxagliptin, alogliptin, linagliptin, gemigliptin and teneligliptin) at any dose and route.

**Comparator:** Placebo or other active agents.

**Study designs to be included:** RCTs with any follow-up duration and sample size were allowed.

**Eligibility criteria:** The criteria for study inclusion were: a) study design: RCTs with any follow-up duration and sample size were allowed; b) population: adult (age ≥ 18 year) patients with a definitive diagnosis of NAFLD or NASH by histologic or imaging evidence (ultrasound, computer tomography or magnetic resonance imaging; c) intervention: GLP-1RAs (liraglutide, exenatide, albiglutide, lixisenatide and dulaglutide) or DPP-IVi (sitagliptin, vildagliptin, saxagliptin, alogliptin, linagliptin, gemigliptin and teneligliptin) at any dose and route; d) control: placebo or other active agents; e) outcomes: primary outcomes are liver histology including steatosis score, hepatocellular ballooning score and lobular inflammation score and liver fat content. Secondary outcomes are liver enzymes including alanine aminotransferase (ALT), aspartate transaminase (AST) and γ-glutamyl transferase (GGT) and adverse events.

**Information sources:** PubMed, Embase, Cochrane Library and Web of Science databases. The reference lists of reviewed articles will be manually searched for additional relevant studies and the ClinicalTrials.gov registry will also be searched for unpublished trials. When incomplete information is available, attempts will be made to contact the study investigators for additional information.

**Main outcome(s):** Liver histology including steatosis score, hepatocellular ballooning score and lobular inflammation score and liver fat content.

**Additional outcome(s):** Liver enzymes including alanine aminotransferase (ALT),

aspartate transaminase (AST) and γ-glutamyl transferase (GGT) and adverse events.

**Data management:** Using a predefined data extraction sheet, two reviewers will independently extract data for review. A third reviewerwill be involved in a discussion for any disagreements. The following information will be extracted from the included studies: first author, published year, study location, study design, inclusion/exclusion criteria, sample size, participants' baseline characteristics, intervention characteristics, control and outcome data.

**Quality assessment / Risk of bias analysis:** Based on the Cochrane Handbook for Systematic Reviews (version 5.3.0), we will assess the methodological quality of all studies. The risks of bias will be classified as low, unclear, or high by evaluating the 7 components as random sequence generation, allocation concealment, blinding of outcome assessment, blinding of participants and personnel, incomplete outcome data, selective outcome reporting, and other bias. Two independent reviewers will conduct this assessment, and a third reviewer will be consulted for any disagreements.

**Strategy of data synthesis:** All statistical analysis will be performed using STATA 15.0 software. We will calculate odds ratio (OR) and 95% confidence intervals (CIs) of outcomes when it is a dichotomous variable. Outcomes will be presented as the weighted mean difference (WMD) and 95% confidence intervals (CIs) when it is a continuous variable. If raw data is not reported, we will impute unreported means ± SDs using established methods via other information (e.g., CIs or median and interquartile range, etc) provided in the publication. If only providing data pre and post-intervention period, we will calculate the change of mean ± SDs using the formula recommended in the Cochrane Handbook Version 5.3.0.

**Subgroup analysis:** Subgroup analysis is prespecified according to intervention drugs (GLP-1Ras or DPP-IVi).

**Sensibility analysis:** Sensitivity analysis will be performed by removing a single trial each time and repeating the meta-analysis to assess the reliability and stability of the pooled results.

**Language:** No.

**Country(ies) involved:** China.

**Keywords:** Nonalcoholic fatty liver disease, incretin-based therapies; protocol; systematic review.

**Dissemination plans:** This review will be published in a journal and disseminated in print by peer-review.

**Contributions of each author:**
Author 1 - Si-min Fan - Conceptualization, Data extraction, Data analysis, Writing – original draft, Writing – review and editing.
Author 2 - Xiao-yan Shi - Data extraction, Writing – original draft.
Author 3 - Yan-ping Fan - Data extraction, Writing – review & editing.
Author 4 - Lin-lin Yang - Data analysis, Software.
Author 5 - Jia Yao - Funding acquisition.
Author 6 - Pei-min Feng - Conceptualization, Methodology, Project administration, Resources.