International Journal of Cardiology 219 (2016) 293–300

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Exenatide in obese or overweight patients without diabetes: A systematic review and meta-analyses of randomized controlled trials

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ARTICLE INFO

Article history:
Received 8 March 2016
Received in revised form 11 May 2016
Accepted 12 June 2016
Available online 15 June 2016

Keywords:
Exenatide
Obesity
Overweight
Body mass index
Meta-analysis

ABSTRACT

Background/objectives: Exenatide, a glucagon-like peptide-1 (GLP-1) receptor agonist, is increasingly used in obese or overweight patients with diabetes. However, its safety profile and effects on weight loss in non-diabetic obese or overweight population remain unclear. We aimed to evaluate efficacy and safety of exenatide in obese or overweight participants without diabetes.

Methods: We searched up to January 2016 in MEDLINE (Ovid SP), EMBASE (Ovid SP), Cochrane Central Register of Controlled Trials (CENTRAL), some Chinese databases and ClinicalTrials.gov for randomized controlled trials (RCTs) investigating exenatide in obese or overweight participants without diabetes. The primary outcomes included body weight and body mass index (BMI). We pooled data to calculate the mean differences (MDs) with their 95% confidence intervals (CIs). We assessed overall evidence quality of BMI reduction and weight loss according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.

Results: Six randomized controlled trials involving 362 patients were included in the meta- analysis. The follow-up duration ranged from 12 to 24 weeks. Compared with control group, a larger body weight loss (MD: −4.47 kg; 95% CI: −6.67 to −2.27; $P < 0.0001$), regardless of dosage and population, was achieved by the obese or overweight patients in exenatide group. Exenatide also elicited a greater reduction in BMI (MD: −0.86 kg/m^2; 95% CI: −1.39 to −0.33; $P = 0.001$) and waist circumferences (MD: −1.78 cm; 95% CI: −3.13 to −0.44; $P = 0.009$) compared with the control. No significant benefits were showed in exenatide group in terms of blood pressure and lipid profiles. Gastrointestinal adverse events were mostly common during the treatment of exenatide.

Conclusions: Exenatide could significantly reduce body weight in obese or overweight participants without diabetes, and might be a safe alternative GLP-1 receptor agonist for weight control in such patients. Larger randomized trials with longer follow-up duration are required to confirm the effectiveness and safety of exenatide.

1. Introduction

Overweight and obesity are established as critical risk factors for various diseases, including cardiovascular diseases, diabetes and malignant tumor [1]. According to a report from World Health Organization (WHO) in January 2015, more than 1.9 billion adults were overweight, among which over 600 million were obese [2]. They are responsible for approximately 2.8 million deaths per year [3].

Recently, a guideline for the medical treatment of obesity released by the Endocrine Society [4] stated that obesity and overweight could be prevented and controlled. For those who could not reduce body weight by lifestyle intervention, oral agents could be considered. Liraglutide (Swxenda®, Novo Nordisk), a glucagon-like peptide-1 (GLP-1) receptor agonist, which is already approved to be a routine treatment for diabetes, has been further permitted by the US Food and Drug Administration (FDA) for weight control in non-diabetic obesity and overweight participants, and is recommended by this guideline [4].

Our previous systematic review indicated that unspecific GLP-1 receptor agonist could reduce the body weight of obese or overweight subjects without diabetes [15]. Among all kinds of GLP-1 receptor agonists, exenatide has a confirmed weight-losing effect in diabetic patients

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http://dx.doi.org/10.1016/j.ijcard.2016.06.028
0167-5273/

[5–7], but is not yet proved to be as effective and safe as its congeneric compounds. Hence we conducted this comprehensive evaluation of exenatide application in obese or overweight subjects without diabetes.

2. Methods

2.1. Literature search

We searched Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (Ovid SP), EMBASE (Ovid SP), VIP Chinese Science and Technique Journals Database, China National Knowledge Infrastructure (CNKI) Database, and Wan Fang Database, for articles published up to 20 January 2016, using the keywords: "exenatide", "obesity" and "overweight". Medical Subject Heading (MeSH) was also used during the search when applicable. ClinicalTrials.gov was also searched for unpublished data. The reference lists of included studies and relevant review articles investigating the use of exenatide in obese and/or overweight patients are screened for potentially eligible studies.

2.2. Study selection

Studies were included if they met the following criteria: (1) randomized controlled trials (RCTs); (2) involving participants with obesity or overweight; (3) using exenatide as the tested agent; (4) published in English; and (5) reporting one of the primary outcomes of interest, namely body weight and body mass index (BMI). Our secondary outcomes of interest were waist circumferences, blood pressure (BP), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c), triglyceride (TG) and adverse events.

2.3. Data extraction

Two authors (NS, YL) reviewed all searched studies independently and extracted data using a pre-defined pilot-tested data extraction form. Discrepancies were resolved through discussion with a third reviewer (SL). The following data were extracted: the last name of the first author, year of publication, sample size, duration of follow-up, intervention strategy, characteristics of participants (total number; diagnose; age; country; body weight; BMI; waist circumference), funding and outcome.

2.4. Quality assessment

The methodological quality of each study included was assessed by two reviewers (NS and YL) independently using the Cochrane Collaboration tool for assessing risk of bias [8], against the following domains: (1) random sequence generation; (2) allocation concealment; (3) blinding of participants and personnel; (4) blinding of outcome assessment; (5) incomplete outcome data; (6) selective reporting; and (7) other sources of bias. Each of them was judged as low risk, high risk and unclear. Discrepancies were resolved by discussion with a third reviewer (SL). We also used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) method to summarize the evidence profiles, concerning inconsistency, indirectness, imprecision, and other sources of bias.

2.5. Statistical analyses

For dichotomous data, we calculated odds ratios (ORs) with their respective 95% confidence intervals (CIs); for continuous outcomes, mean differences (MDs) with their 95% respective confidence intervals

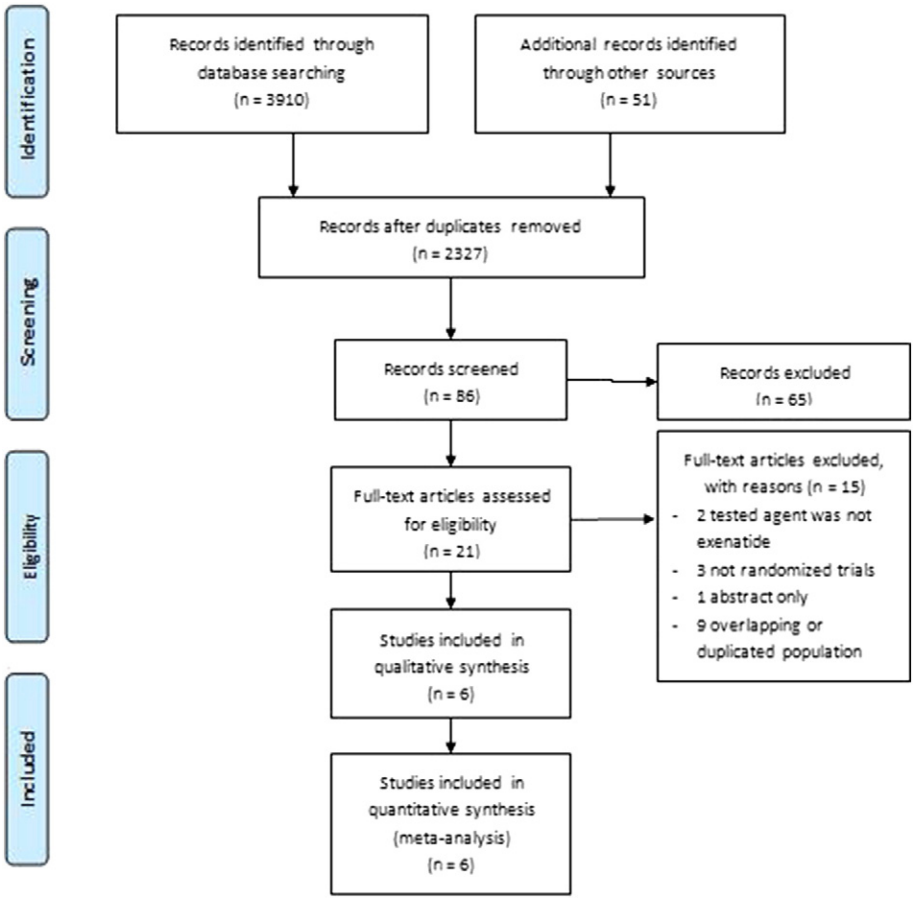

Fig. 1. Flow diagram for study identification and inclusion (PRISMA Flow Diagram).