The effect of metformin on weight and other metabolic parameters and outcomes in obese non-diabetic patients: a systematic review and meta-analysis of randomized controlled trials

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Review question

1- Comparing metformin to placebo/control or to any other drug therapy, assess the effect on weight loss and the proportion of patients reaching at least 5% weight loss

2- Comparing metformin to placebo/control or to any other drug therapy, assedd the effect on other metabolic and cardio-vascular parameters and outcomes.

Searches

The search was conducted, in October 2017, in MEDLINE (1946 to present), EMBASE, PubMed and the The Cochrane Library without time or language limitation.

Search strategy

https://www.crd.york.ac.uk/PROSPEROFILES/85512_STRATEGY_20180823.pdf

Types of study to be included

-Inclusion criteria:

Randomized controlled trials.

English, French, Spanish, Portuguese, Persian and German articles.

Published and unpublished data.

No publication date restriction.

-Exclusion criteria:

Prospective interventional studies that are not randomized and single arm studies.

Condition or domain being studied

Obesity has reached alarming rates (WHO Obesity Fact Sheet; Abacra-Gomez 2017; Shettar 2017). According to the National Health and Nutrition Examination Survey (NHANES), the prevalence of obesity has risen significantly in the US, comparing the period 2013-2014, to the period 1999-2000 (Ogden 2015). More than a third of adult US individuals have a BMI > 30 kg/m2 (Ogden 2015). The Global Burden of Disease (GBD) study systematically collected data on body mass index (BMI) from representative studies conducted in 195 countries, and reported an obesity rate of 5% in children and 12% in adults (Afshin 2017). Obesity increases the risk of various non-communicable diseases (NCDs), diabetes mellitus, cancer, cardio-vascular diseases and others (Guh 2009), and this would translate into a higher all-cause mortality (Afshin 2015). Obesity implies a socio-economic burden, with increased health services costs, in addition to indirect costs, secondary to absenteeism from work, lower wages and lower income (https://www.hsph.harvard.edu/obesity-prevention-source/obesity-consequences/economic/)

Participants/population

-Inclusion criteria:

Studies conducted in overweight or obese adults (mean BMI of participants in individual study ? 25 kg/m2).

-Exclusion criteria

Studies conducted in diabetic patients (?75% of the population).

Studies conducted in obese patients who underwent bariatric surgery.

Studies conducted in patients with polycystic ovaries syndrome, HIV or on weight-gain inducing medications, such as anti-psychotics (in ? 75% of the population).

Studies conducted on pregnant women

Intervention(s), exposure(s)

-Inclusion criteria:

Metformin therapy, at any dose, taken at least for 3 months, compared to any other drug therapy or placebo, with or without concomitant lifestyle changes.

-Exclusion criteria:

Studies were co-intervention (lifestyle changes, including dietary modifications and exercise) differed between arms.

Studies that did not provide a detailed description of the intervention (dose and duration).

Studies where other weight loss medication was given concomitantly with Metformin

Comparator(s)/control

-Inclusion criteria

Any non-surgical intervention or placebo taken for the same duration as metformin.

Context

Main outcome(s)

Percent weight loss and the proportion of patients reaching at least 5% weight loss, comparing metformin to placebo/control or to any other active comparator; analysis for each comparison being done separately.

Timing and effect measures

We will calculate the Mean Difference (MD), and 95% confidence interval, in the percent weight loss achieved at the end of the intervention, and estimate the proportion of patients reaching at least 5% weight loss, comparing metformin to placebo/control or to any other active comparator. The analysis for each comparison will be performed separately.

Additional outcome(s)

Waist circumference, glycemic parameters, lipid profile, body composition, bone mineral density, liver function tests, liver fat content, microalbuminuria, satiety and hunger indices, blood pressure, muscle strength, fractures, mortality rate, adverse events.

Timing and effect measures

Comparing metformin to placebo/control:

For continuous variables, we will calculate the MD and 95% confidence interval.

For categorical variables, we will calculate the RR and 95% confidence interval.

Data extraction (selection and coding)

Risk of bias (quality) assessment

We will review the retrieved titles and abstracts in duplicate and independently. We will use the PICO question for the screening of titles and abstracts. We will retrieve the full text of all citations included by at least one reviewer. We will conduct full text screening in duplicate and independently, using a standardized form. We will conduct a calibration exercise on a sample of titles and abstracts and full texts, in order to insure that all the reviewers' screening process is standardized. We will solve disagreement at the level of full text screening by discussion with an expert author. We will develop data collection sheets a priori and we will pilot-test them on few articles, in order to refine them as needed. We will perform duplicate and independent data collection. We will solve disagreement between reviewers by discussion.

We will extract data on the characteristics of the population (age, sex, baseline BMI,co-morbidities, blood pressure, glycemic parameters, body composition, bone density, satiety and hunger indices).

We will extract also data on the characteristics of the intervention (dose, frequency, compliance), and the outcomes, as defined in section above.

Strategy for data synthesis

We will express continuous outcomes as mean difference (MD) with 95% confidence interval (CI). We will express dichotomous outcomes using Relative Risk (RR) and Hazard Ratio (RR) and 95% CI. We will conduct a meta-analysis when at least 2 studies are available in each comparison: MTF versus placebo or control, MTF versus any other comparator (comparison with each comparator being analyzed separately). We will analyze data comparing metformin to each specific active comparator or placebo/control separately. Studies will be analyzed separately depending on whether the intervention included lifestyle changes or not. In case we identify ? 10 studies in a given comparison, we will conduct a meta-regression to identify the predictors of weight loss in response to metformin therapy. We will use a random effects model for the primary analysis. We will conduct the analysis on Review Manager Version 3.

Analysis of subgroups or subsets

In case of heterogeneity, pre-specified sub-group analysis will be performed, based on the following potential predictors:

- Age: age <60 years versus age ? 60 years.

- Baseline BMI: BMI < 35 kg/m2; BMI ? 35 kg/m2.

- Glycemic status (Pre diabetes versus normal glucose), as per the ADA criteria (4).

- Study duration (< 6 months versus ? 6 months).

Contact details for further information

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Anticipated or actual start date
04 September 2017

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15 December 2018

Funding sources/sponsors
No funding.

Conflicts of interest

Language
(there is not an English language summary)

Country
Lebanon

Published protocol
https://www.crd.york.ac.uk/PROSPEROFILES/85512_PROTOCOL_20180823.pdf

Stage of review
Review_Ongoing

Subject index terms status
Subject indexing assigned by CRD

Subject index terms
Body Weight; Humans; Metformin; Obesity

Date of registration in PROSPERO
19 January 2018

Date of publication of this version
20 September 2018

Details of any existing review of the same topic by the same authors

Stage of review at time of this submission

Stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

Versions
19 January 2018
07 February 2018

25 April 2018
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