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

Chakhtoura M, Zarzour F, Saadeh N, Ghosn A, Mantzoros C

Abstract

Background

Obesity has reached alarming rates. Several pharmacologic drug therapies are approved for medical weight loss, and several others are used off-label.

Metformin (MTF) is one of the oldest oral hypoglycemic agents, and is still the first line therapy according to the latest diabetes management guidelines. MTF has demonstrated weight-reducing effects, not only in the diabetic population, but also in patients with polycystic ovaries, and patients on anti-psychotics. Furthermore, moderate weight reduction was reported in trials using MTF in obese non-diabetic patients. Given the increased off-label use of MTF as an anti-obesity agent in the latter population, for its high safety profile and low cost, it is important to review and scrutinize the available trials on the topic, and identify the patient's profile predicting the best response to this intervention.

Objectives

The primary objective is to assess the mean difference in the percent weight loss and the proportion of patients reaching >5% weight loss, comparing MTF to placebo/control or to any other drug therapy. The secondary objectives are to assess the effect of MTF on other metabolic and cardio-vascular parameters and outcomes.

Materials and methods

Eligibility criteria

We will include randomized controlled trials, conducted in overweight and obese non-diabetic adult individuals, administering metformin, at any dose, for at least 3 months duration, with and without concomitant lifestyle changes.

Data sources

We will conduct a systematic search in the following databases: Medline, PubMed, Embase, and the Cochrane Library, without time restriction. We will include only English articles.

Study selection

We will review the titles and abstracts of the retrieved citations, in duplicate and independently, based on the PICO question. We will review the full text of the potential papers, in duplicate and independently, using standardized forms, and after a calibration exercise to insure standardization of articles' screening among reviewers. We will solve discrepancies by discussion or by consultation with an expert author.

Data extraction

We will collect data on pertinent variables related to the intervention, population and outcomes, using data collection sheets, prepared a priori.

Risk of bias

We will assess the risk of bias (ROB) using the 2011 Cochrane ROB tool. We will assess the risk of publication bias using the funnel plot.

Primary analysis and additional analysis

The primary analysis will be done using a random-effects model. 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 active comparator; studies on each active comparator being analyzed separately.
We will conduct also additional sub-group analyses according to age, baseline BMI, baseline glucose status and study duration.

Summary measures

We will express continuous outcomes and dichotomous outcomes, as mean differences (MD) and risk ratio (RR) or hazard ratio (HR), respectively, with 95% confidence interval (CI).

Discussion

This systematic review aims at revisiting the beneficial effects of Metformin, in terms of weight loss and improvement in other metabolic parameters. Given its availability, safety profile and affordable price, metformin can be considered as an intervention in the battle against the rapidly increasing rates of obesity at the public health level.

Background

Obesity Prevalence and Co-morbidities

Obesity has reached alarming rates (1-3). 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 (4). More than a third of adult US individuals have a BMI > 30 kg/m^2 (4). The Global Burden of Disease (GBD) study systematically collected data on body mass index (BMI) from 195 epidemiologic studies conducted worlwide, and reported an obesity rate of 5% in children and 12% in adults (5). Obesity increases the risk of various non-communicable diseases (NCDs), diabetes mellitus, cancer, cardio-vascular diseases and others (6), and this would translate into a higher all-cause mortality (5). Obesity implies a socio-economic burden, with increased health services costs, in addition to indirect costs, related to absenteeism from work, lower wages and lower income (7).

Medical Weight Management

While lifestyle modifications (diet, exercise and behavioral therapy) remain the cornerstone of any weight management approach, the FDA has approved, in the last couple of years, several pharmacologic therapies for medical weight loss (8). These drugs include: Orlistat, Lorcaserin, Liraglutide, and the combinations, Phentermine/Topamax and Naltrexone/Bupropion (9). Several other drugs, such as Metformin, are being used off-label for weight loss, given their availability, high safety profile and low cost (10).

Metformin use in diabetes mellitus

Metformin (MTF), dimethybiguanide, is a drug derived from herbal extracts, *Galega officinalis* that was initially used in Europe to treat several diseases, including plague, worms and others (11). The drug was developed in 1957, and was described as a *"glucose eater"*, and therefore, named as *"Glucophage"* (11). MTF is considered the safest among other biguanides (12).

Diabetes treatment guidelines recommend MTF as a first line therapy (13, 14), given its efficacy, low cost, safety profile and evidence of cardiovascular protection (13, 14). Indeed, MTF has been shown to improve HbA1c by 0.8-3%, depending on the dose and the baseline HbA1c level (15). It is the oldest hypoglycemic agent with proven prevention of diabetic complications. In the landmark UKPDS study, MTF, compared to conventional therapy, resulted in a 32% reduction in a composite outcome of diabetes related clinical endpoints, defined as follows: sudden death, death from hyperglycaemia or hypoglycaemia, fatal or non-fatal myocardial infarction, angina, heart failure, stroke, renal failure, amputation (of at least one digit), vitreous hemorrhage, retinopathy requiring photocoagulation, blindness in one eye, or cataract extraction (16). As an add-on to insulin, and compared to placebo in the HOME trial, MTF allowed a 40% reduction in the macrovascular endpoints, not only through an improvement in glycemic control, but also secondary to weight reduction, and potentially other mechanisms (17). In a meta-analysis of randomized trials, metformin, compared to control or placebo in 18 studies, showed a significant reduction in cardiovascular events (fatal or non-fatal myocardial infarction, stroke and peripheral artery disease), by 21% (p 0.031), and in mortality by 45% (p 0.014), especially in the younger population and in studies of > 1 year duration (18). However, the authors' conclusion was that these protective effects are most likely mediated by glycemic control, rather than other mechanisms (18).

Metformin for weight loss

- Diabetic patients

In diabetic patients with excess weight, the American Diabetes Association (ADA) recommends the use of one of the weight loss promoting agents, MTF or one of the newer medications, sodium–glucose cotransporter 2 inhibitors (SGLT2), glucagon-like peptide 1 agonists (GLP1), or amylin mimetics (14). Indeed, in diabetic patients, MTF results in a significant weight loss (range of mean difference in weight loss -1.3 to -2.7 kg), compared to sulfonylurea, thiazolidinedione and DPP-IV inhibitors (19).

- Non-diabetic patients

Polycystic Ovary Syndrome (PCOS) is characterized by increased androgens, and ovulatory dysfunction, in addition to insulin resistance and other metabolic disorders (20). Metformin is recommended in PCOS patients, as a first line therapy, in patients with diabetes mellitus or impaired fasting glucose, and as a second line therapy, in patient with irregular menses who cannot take hormonal contraception (20). In this population, MTF allows 1.3-5.4 kg weight loss, at 3-8 months, and resumption of regular menses in 36-91% of patients (21-23). Conversely, the effect of MTF on dermatologic manifestations, hirsutism and acne, is less potent and inadequately evaluated (24).

Anti-psychotic medications are known to induce weight gain and metabolic changes, with a wide variation between specific drugs (25). Clozapine and Olanzapine are the most notoriously associated with weight gain, whereas ziprasidone and aripiprazole have the lowest risk (25). A systematic review and meta-analysis of randomized controlled trials (RCTs) on pharmacologic interventions for the treatment of anti-psychotic induced weight gain showed that MTF was the most commonly used drug in these patients (26). MTF yielded a significant weight loss of -2.94 kg (-4.89;-0.99), p 0.003, compared to placebo (26). Weight loss with other drugs, including sibutramine, topiramate, fenfluramine and reboxetine, was significantly different from placebo, but to a lesser extent, compared to MTF (16). Furthermore, in 2 studies, MTF resulted in a significant reduction in the risk of gaining $\geq$ 7% of baseline weight (RR 0.24 (CI 0.09; 0.62), p 0.003 (26). Other recent systematic reviews of RCTs followed and confirmed the efficacy of MTF, compared to placebo, in the prevention and treatment of anti-psychotics induced weight gain (27-30). In addition to improving insulin sensitivity, MTF improves lipid disorders (30), and may potentially play a role centrally, by interfering with histamine receptor (27); the latter mechanism still needs to be confirmed.

Metformin has been used for weight loss in obese non-diabetic adults (31, 32). In the Diabetes Prevention Program (DPP), MTF resulted in a significant weight loss compared to placebo (2.1(5.6)% in the MTF arm versus 0.02(5.5)% in the control arm, $p < 0.001$); the effect persisted over the 7-8 years follow up period (33, 34). One systematic review of 9 trials (search period until year 2003), conducted in non-diabetic patients (mean BMI 30-48 kg/m^2), showed that MTF-induced weight loss ranges between 0.5 and 3.6 kg, at an average dose of 850 mg twice daily, over 2-12 months (31). The limitations of the later review, and as recognized by the authors, were related to the lack of power in some included individual trials, and the short duration (intervention for less than 3 months in 3 studies) (31). Another similar systematic review (search period until year 2008) identified 5 trials, showing that weight loss with metformin in non-diabetic patients (mean BMI >30 kg/m^2), assessed as a primary outcome, was -0.5 to -9 kg, with a dose ranging between 500 to 850 mg three times per day (35). Conversely, in studies where

weight loss with MTF was assessed as a secondary outcome (mean BMI 29-33 kg/m^2), weight loss was less, varying between -0.5 and -3 kg (35). A recent prospective study from Germany, comparing MTF to controls, without a dietary program, in a population of young adults, with a mean BMI of 35 kg/m^2, showed a significant weight loss in the former group, of 5.6 (6.5)%, and 47% of participants lost at least 5% of their weight (36). Interestingly, weight loss did not occur only in patients with insulin resistance, but also in insulin sensitive patients, suggesting other potential mechanisms contributing to weight loss with MTF use (36).

Potential mechanisms of Metformin-induced weight loss

Improvement in insulin sensitivity is a well-known mechanism, through which MTF, improves glucose control and promotes weight loss (37). In addition, several other central and peripheral potential pathways could facilitate MTF induced weight loss (37).

- Effect on the central nervous system

Data on the effects of MTF on visceral and central nervous system are derived mostly from rodent models. One study showed that MTF reduces the portion size and the meals number in obese mice (38). Such effects may be mediated by the activation of the nucleus tractus solitaries; the latter being connected to various neuro-circuits involved in food intake and energy status (38). MTF can modulate the activity of orexigenic pathways in the hypothalamus, specifically by decreasing the activity of neuropeptide Y (NPY) and agouti-related protein (AgRP) (39). In addition, a leptin sensitizing effect of MTF at the level of the arcuate nucleus was described in fat fed obese rats (40, 41). MTF also decreases ghrelin levels (37). Finally, improved insulin sensitivity, a well-known effect of MTF, may potentially contribute to the amelioration in anorexia signaling centrally (42). Interestingly, in diabetic obese patients, MTF resulted in decreased appetite and hunger, in a dose dependent manner (43).

- Effect on the gastrointestinal tract, gut hormones, muscle and adipose tissue

In the gastro-intestinal tract, MTF was shown to act at various levels in diabetic patients (44, 45). It reduces glucose absorption at the enterocytes and increases glucose utilization (44, 46). In addition, it increases satiety by increasing GLP1 levels, in both diabetic and non-diabetic patients, possibly by directly enhancing its secretion (44), or by inhibiting the dipeptidyl peptidase IV activity (47). MTF also inhibits bile acid reabsorption, and this could potentially increase GLP1 levels (48). MTF is known to decrease hepatic gluconeogenesis and hepatic lipids synthesis (37). Similarly, in the muscle, MTF stimulates glucose uptake and fat oxidation (37). Indeed, this improvement in peripheral glucose uptake is known to be mediated by enhanced insulin sensitivity (37). MTF improves energy metabolism, through the phosphorylation of the AMP activated protein kinase system (AMPK) (37). The latter pathway facilitates the hepatic and skeletal benefits, in addition to decreasing lipid synthesis and storage, yielding effects similar to what happens after exercise (37). Conversely, the effect of MTF on gastric emptying has not been proven yet (39). Recent data showed that MTF could alter gut microbiome, as it was shown in mouse model, rendered obese with a high fat diet, in which treatment with MTF increased specific species (Akkermansia muciniphila and Clostridium cocleatum) (40)

Given the increasing off-label use of MTF for weight control in non-diabetic patients (10), and given that the previous systematic reviews of trials did not generate firm conclusions regarding the weight-reducing

effects of MTF, mostly related to low quality studies, short duration and lack of power, it is important to update the previous results and look at the evidence with more scrutiny. In addition, to our knowledge, the potential beneficial effects of MTF on body composition, fatty liver and other cardiovascular and metabolic parameters, including blood pressure, and lipid profile, in non-diabetic patients, have not been systematically evaluated.

Aim

Our aim is to assess, in obese non-diabetic patients, the effect of MTF, compared to control or any other active comparator, on weight loss and metabolic and cardio-vascular parameters.

Methods

1- Eligibility criteria

a- Type of studies:

-Inclusion criteria:

RCTs
English articles
Published data
No publication date restriction

-Exclusion criteria:

Prospective interventional studies that are not randomized and single arm studies

b- Population

-Inclusion criteria:

Studies conducted in overweight or obese adults (mean BMI of participants in individual study ≥ 25 kg/m^2)

-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 (≥ 75% of the population)
Studies conducted in pregnant women

c- Intervention

-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 where co-intervention (lifestyle changes, including dietary modifications and exercise) differs between arms
Studies that did not provide a detailed description of the intervention (dose and duration)

d- Comparator

-Inclusion criteria

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

e- Outcomes

-Inclusion criteria

Studies reporting on the quantitative effect(s) of the intervention on weight, metabolic parameters or adverse events (as described in the following section)

2- Outcome measures

-Primary outcome measure:

Mean difference in the percent weight loss and estimate the proportion of patients reaching ≥ 5% weight loss, comparing metformin to placebo/control or to any other active comparator; analysis for each comparison being done separately.

-Secondary outcomes:

Comparing metformin to control/placebo or any other active comparator, we will evaluate the mean difference in the change (or percent difference) or the mean difference in level achieved post-intervention in the following outcomes:

- Waist circumference
- BMI
- Weight
- Compliance rate
- Glycemic parameters: Fasting glucose, fasting insulin, glycosylated hemoglobin, HOMA indices
- Leptin, GLP1, ghrelin levels
- Blood pressure parameters: systolic and diastolic blood pressure
- Lipid profile: HDL, LDL, TG, Total cholesterol
- Liver function tests: ALT, AST, GGT, ALT or hepatic fat content assessed by US or MRI
- CRP
- Muscle strength
- Bone density at various sites
- Body composition: fat mass and lean mass
- Satiety and hunger indices

In addition, comparing metformin to control/placebo or any other active comparator, we will assess the relative risk of the following:

- Adverse events
- Fractures
- Mortality

3- Information sources and literature search

We will conduct a systematic search in the following database, without time restriction: Medline, PubMed, Embase, and the Cochrane Library. We will use Mesh Terms and keywords relevant to obesity, overweight, metformin and randomized trials, in non-diabetic patients. For full details of the search strategy, see Appendix 1.

4- Study selection

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.

5- Data collection process and data items

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.
Figure 1 represents the flow diagram of the systematic review.

6- Data items

We will abstract data from each trial on the following characteristics:

a- Characteristics of study population

-Author/year
-Country of origin
-Age
-Sex
-Baseline BMI
-Baseline waist circumference
-Baseline co-morbidities
-Baseline blood pressure
-Baseline lipid profile
-Baseline liver function test
-Baseline glycemic parameters: Fasting glucose, fasting insulin, glycosylated hemoglobin, HOMA index
-Baseline CRP
-Baseline micro-albuminuria
-Baseline muscle strength
-Baseline bone density at various sites
-Baseline body composition: fat mass and lean mass
-Baseline satiety and hunger indices

b- Characteristics of intervention:

-Dose of metformin
-Frequency of metformin

-Duration of metformin
-Compliance
-Presence or absence of concomitant intervention
-Comparator used
Placebo
Other drug: Type, Dose, frequency

c- Characteristics of the outcome measure, per each treatment arm, being expressed as level post intervention or change (or percent change) in level:
-Percent weight loss
-Waist circumference
-BMI
-Compliance rate
-Glycemic parameters: Fasting glucose, fasting insulin, glycosylated hemoglobin, HOMA index
-Blood pressure parameters: systolic and diastolic blood pressure
-Lipid profile: HDL, LDL, TG, Total cholesterol
-Liver function tests: ALT, AST, GGT, ALT or hepatic fat content assessed by US or MRI
-CRP level
-Micro-albuminuria
-Muscle strength
-Bone density at various sites
-Body composition: fat mass and lean mass
-Satiety and hunger indices
-Adverse events
-Fractures
-Mortality

We will also collect information on the proportion of patients reaching a weight loss ≥ 5%. In case these information are not provided, the proportion will be calculated as described in the method section

7- Risk of bias across studies

Two reviewers will assess the risk of bias of each individual study, in duplicate and independently, using the Cochrane Collaboration's tool 2011 (49). The latter tool evaluates the following domains: adequacy of sequence generation, concealment of allocation, blinding of participants and personnel, blinding of outcome assessors, extent of loss to follow-up (incomplete outcome data), selective outcome reporting and other sources of bias (49). For each domain, judgment will be done qualitatively, answered as yes/no/unclear, based on answering a specific question, and as described in the Cochrane Handbook (49). An answer "yes" indicates a low risk of bias. An answer "No" indicates a high risk of bias. "Unclear" judgment is made when the risk of bias in unknown.
We will assess the risk of publication bias using a funnel plot of included studies.

8- Quality of evidence assessment

For the primary outcome, we will assess the quality of evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) (50).

9- Summary measure and analysis plan

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. 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.

We will estimate the proportion of individuals reaching a weight loss ≥ 5%, by calculating the weighted mean (WM) percent weight loss across arms of a given comparison and the corresponding pooled standard deviation (SDp) of weight loss, and assuming normal distribution of the percent weight loss variable.

We will calculate the WMs and their pooled standard deviations (SDp) using the following formulas:

- WM = (n1 m1 + n2 m2 + …. + ni mi) / (n1 + n2 +..+ ni) (44)
- SDp =sqrt[[(n1-1)$(SD1)^2$ +(n2-1)$(SD2)^2$+…+ (ni-1)$(SDi)^2$] / [(n1-1)+(n2-1)+…+(ni-1)]](45)

where “n” is the number of participants per arm; “m” is the mean percent weight loss and “SD” is the standard deviation of the percent weight loss in each study arm.

In case, percent weight loss is not provided in an individual study, we will contact the corresponding author by email, requesting results on this variable.

Assessment of heterogeneity

We will assess heterogeneity using Chi square with significance at p-value ≤ 0.1, and quantitatively using I^2. 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/m^2; BMI ≥ 35 kg/m^2
- Glycemic status (Pre diabetes versus normal glucose), as per the ADA criteria (4)
- Study duration (< 6 months versus ≥ 6 months)

Discussion

Given the increasing off-label use of MTF for weight management, this systematic review will update results of previous reviews on the topic, and will shed light on MTF-induced beneficial metabolic effects, beyond glycemic control. Given its affordable price and safety, MTF should be considered among the weight loss inducing medications, specifically in patients who have contra-indications or cannot afford other interventions.

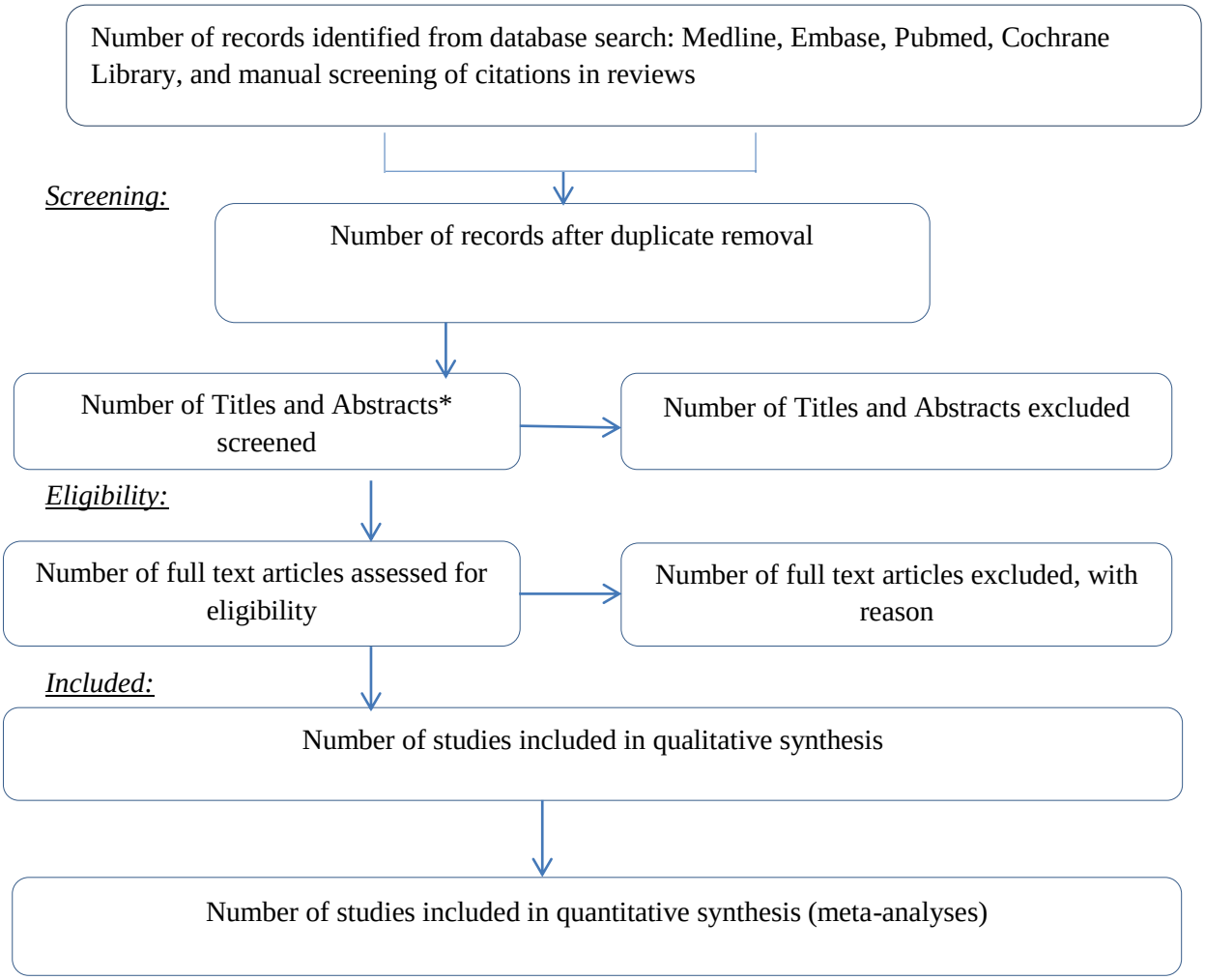
References

1. WHO Obesity and Overweight Fact Sheets. Available from (accessed in January 2018): http://www.who.int/mediacentre/factsheets/fs311/en/.
2. Abarca-Gómez L, Abdeen ZA, Hamid ZA, Abu-Rmeileh NM, Acosta-Cazares B, Acuin C, et al. Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128·9 million children, adolescents, and adults. The Lancet. 2017;390(10113):2627-42.
3. Shettar V, Patel S, Kidambi S. Epidemiology of Obesity and Pharmacologic Treatment Options. Nutrition in Clinical Practice. 2017;32(4):441-62.
4. Ogden CL, Carroll MD, Fryar CD, Flegal KM. Prevalence of obesity among adults and youth: United States, 2011-2014: US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics; 2015.
5. Afshin A, Forouzanfar MH, Reitsma MB, Sur P, Estep K, Lee A, et al. Health effects of overweight and obesity in 195 countries over 25 years. The New England Journal of Medicine. 2017;377(1):13-27.
6. Guh DP, Zhang W, Bansback N, Amarsi Z, Birmingham CL, Anis AH. The incidence of co-morbidities related to obesity and overweight: a systematic review and meta-analysis. BMC Public Health. 2009;9(1):88.
7. Obesity Consequences. Available from (accessed in January 2018): https://www.hsph.harvard.edu/obesity-prevention-source/obesity-consequences/economic.
8. Bray GA, Frühbeck G, Ryan DH, Wilding JP. Management of obesity. The Lancet. 2016;387(10031):1947-56.
9. Apovian CM, Aronne LJ, Bessesen DH, McDonnell ME, Murad MH, Pagotto U, et al. Pharmacological management of obesity: an Endocrine Society clinical practice guideline. The Journal of Clinical Endocrinology & Metabolism. 2015;100(2):342-62.
10. Hendricks EJ. Off-label drugs for weight management. Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy. 2017;10:223.
11. Bailey CJ, Day C. Metformin: its botanical background. Practical Diabetes. 2004;21(3):115-7.
12. Howlett HC, Bailey CJ. A risk-benefit assessment of metformin in type 2 diabetes mellitus. Drug Safety. 1999;20(6):489-503.
13. Garber AJ, Abrahamson MJ, Barzilay JI, Blonde L, Bloomgarden ZT, Bush MA, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm–2016 executive summary. Endocrine Practice. 2016;22(1):84-113.
14. Marathe PH, Gao HX, Close KL. American Diabetes Association standards of medical care in diabetes 2017. Journal of Diabetes. 2017;9(4):320-4.
15. Bosi E. Metformin–the gold standard in type 2 diabetes: what does the evidence tell us? Diabetes, Obesity and Metabolism. 2009;11(s2):3-8.
16. Group UKPDS. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). The Lancet. 1998;352(9131):854-65.
17. Kooy A, de Jager J, Lehert P, Bets D, Wulffelé MG, Donker AJ, et al. Long-term effects of metformin on metabolism and microvascular and macrovascular disease in patients with type 2 diabetes mellitus. Archives of Internal Medicine. 2009;169(6):616-25.
18. Lamanna C, Monami M, Marchionni N, Mannucci E. Effect of metformin on cardiovascular events and mortality: a meta-analysis of randomized clinical trials. Diabetes, Obesity and Metabolism. 2011;13(3):221-8.
19. Qaseem A, Barry MJ, Humphrey LL, Forciea MA. Oral Pharmacologic Treatment of Type 2 Diabetes Mellitus: A Clinical Practice Guideline Update From the American College of

PhysiciansOral Pharmacologic Treatment of Type 2 Diabetes Mellitus. Annals of Internal Medicine. 2017;166(4):279-90.
20. Azziz R, Carmina E, Dewailly D, Diamanti-Kandarakis E, Escobar-Morreale HF, Futterweit W, et al. Criteria for defining polycystic ovary syndrome as a predominantly hyperandrogenic syndrome: an androgen excess society guideline. The Journal of Clinical Endocrinology & Metabolism. 2006;91(11):4237-45.
21. Harborne LR, Sattar N, Norman JE, Fleming R. Metformin and weight loss in obese women with polycystic ovary syndrome: comparison of doses. Journal of Clinical Endocrinology & Metabolism. 2005;90(8):4593-8.
22. Glueck C, Fontaine R, Wang P, Subbiah M, Weber K, Illig E, et al. Metformin reduces weight, centripetal obesity, insulin, leptin, and low-density lipoprotein cholesterol in nondiabetic, morbidly obese subjects with body mass index greater than 30. Metabolism. 2001;50(7):856-61.
23. Ravn P, Haugen A, Glintborg D. Overweight in polycystic ovary syndrome. An update on evidence based advice on diet, exercise and metformin use for weight loss. Minerva Endocrinology 2013;38(1):59-76.
24. Diamanti-Kandarakis E, Economou F, Palimeri S, Christakou C. Metformin in polycystic ovary syndrome. Annals of the New York Academy of Sciences. 2010;1205(1):192-8.
25. Roerig JL, Steffen KJ, Mitchell JE. Atypical antipsychotic-induced weight gain. CNS drugs. 2011;25(12):1035-59.
26. Maayan L, Vakhrusheva J, Correll CU. Effectiveness of medications used to attenuate antipsychotic-related weight gain and metabolic abnormalities: a systematic review and meta-analysis. Neuropsychopharmacology. 2010;35(7):1520-30.
27. Zheng W, Li X-B, Tang Y-L, Xiang Y-Q, Wang C-Y, de Leon J. Metformin for weight gain and metabolic abnormalities associated with antipsychotic treatment: meta-analysis of randomized placebo-controlled trials. Journal of Clinical Psychopharmacology. 2015;35(5):499-509.
28. De Silva VA, Suraweera C, Ratnatunga SS, Dayabandara M, Wanniarachchi N, Hanwella R. Metformin in prevention and treatment of antipsychotic induced weight gain: a systematic review and meta-analysis. BMC Psychiatry. 2016;16(1):341.
29. Bjorkhem-Bergman L, Asplund AB, Lindh JD. Metformin for weight reduction in non-diabetic patients on antipsychotic drugs: a systematic review and meta-analysis. Journal of Psychopharmacology. 2011;25(3):299-305.
30. Siskind DJ, Leung J, Russell AW, Wysoczanski D, Kisely S. Metformin for clozapine associated obesity: a systematic review and meta-analysis. PloS One. 2016;11(6):e0156208.
31. Levri KM, Slaymaker E, Last A, Yeh J, Ference J, D'Amico F, et al. Metformin as treatment for overweight and obese adults: a systematic review. The Annals of Family Medicine. 2005;3(5):457-61.
32. Hamman RF, Wing RR, Edelstein SL, Lachin JM, Bray GA, Delahanty L, et al. Effect of weight loss with lifestyle intervention on risk of diabetes. Diabetes Care. 2006;29(9):2102-7.
33. Group DPPR. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. New England Journal of Medicine. 2002;2002(346):393-403.
34. Group DPPR. Long-term safety, tolerability, and weight loss associated with metformin in the Diabetes Prevention Program Outcomes Study. Diabetes Care. 2012;35(4):731-7.
35. Desilets AR, Dhakal-Karki S, Dunican KC. Role of metformin for weight management in patients without type 2 diabetes. Annals of Pharmacotherapy. 2008;42(6):817-26.
36. Seifarth C, Schehler B, Schneider H. Effectiveness of metformin on weight loss in non-diabetic individuals with obesity. Experimental and Clinical Endocrinology & Diabetes. 2013;121(01):27-31.
37. Igel L, Sinha A, Saunders K, Apovian C, Vojta D, Aronne L. Metformin: an old therapy that deserves a new indication for the treatment of obesity. Current Atherosclerosis Reports. 2016;18(4):16.

38. Kim H-J, Zhang X-H, Park E-Y, Shin K-H, Choi S-H, Chun B-G, et al. Metformin decreases meal size and number and increases c-Fos expression in the nucleus tractus solitarius of obese mice. Physiology & Behavior. 2013;110:213-20.
39. Lv W-s, Wen J-p, Li L, Sun R-x, Wang J, Xian Y-x, et al. The effect of metformin on food intake and its potential role in hypothalamic regulation in obese diabetic rats. Brain research. 2012;1444:11-9.
40. Aubert G, Mansuy V, Voirol M-J, Pellerin L, Pralong FP. The anorexigenic effects of metformin involve increases in hypothalamic leptin receptor expression. Metabolism. 2011;60(3):327-34.
41. Kim Y-W, Kim J-Y, Park Y-H, Park S-Y, Won K-C, Choi K-H, et al. Metformin restores leptin sensitivity in high-fat–fed obese rats with leptin resistance. Diabetes. 2006;55(3):716-24.
42. Malin SK, Kashyap SR. Effects of metformin on weight loss: potential mechanisms. Current Opinion in Endocrinology, Diabetes and Obesity. 2014;21(5):323-9.
43. Lee A, Morley JE. Metformin decreases food consumption and induces weight loss in subjects with obesity with type II non-insulin-dependent diabetes. Obesity. 1998;6(1):47-53.
44. Wu T, Xie C, Wu H, Jones KL, Horowitz M, Rayner CK. Metformin reduces the rate of small intestinal glucose absorption in type 2 diabetes. Diabetes, Obesity and Metabolism. 2017;19(2):290-3.
45. Wu H, Esteve E, Tremaroli V, Khan MT, Caesar R, Mannerås-Holm L, et al. Metformin alters the gut microbiome of individuals with treatment-naive type 2 diabetes, contributing to the therapeutic effects of the drug. Nature Medicine. 2017.
46. Viollet B, Guigas B, Garcia NS, Leclerc J, Foretz M, Andreelli F. Cellular and molecular mechanisms of metformin: an overview. Clinical Science. 2012;122(6):253-70.
47. Lindsay J, Duffy N, McKillop A, Ardill J, O'harte F, Flatt P, et al. Inhibition of dipeptidyl peptidase IV activity by oral metformin in Type 2 diabetes. Diabetic medicine. 2005;22(5):654-7.
48. Mannucci E, Ognibene A, Cremasco F, Bardini G, Mencucci A, Pierazzuoli E, et al. Effect of metformin on glucagon-like peptide 1 (GLP-1) and leptin levels in obese nondiabetic subjects. Diabetes Care. 2001;24(3):489-94.
49. Maida A, Lamont B, Cao X, Drucker D. Metformin regulates the incretin receptor axis via a pathway dependent on peroxisome proliferator-activated receptor-α in mice. Diabetologia. 2011;54(2):339-49.39.
50. Lee H, Ko G. Effect of metformin on metabolic improvement and gut microbiota. Applied and Environmental Microbiology. 2014;80(19):5935-43.
51. Hendricks EJ. Off-label drugs for weight management. Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy. 2017;10:223.
52. Higgins JP, Green S. Cochrane handbook for systematic reviews of interventions: John Wiley & Sons; 2011.
53. Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M, et al. GRADE guidelines: 8. Rating the quality of evidence—indirectness. Journal of Clinical Epidemiology. 2011;64(12):1303-10.
54. http://www.statisticshowto.com/weighted-mean/. (Accessed in January 2018)
55. https://www.isixsigma.com/dictionary/pooled-standard-deviation/. (Accessed in January 2018)

Figure: Flow diagram of different steps of the systematic review



Appendix 1: Search strategy

Medline:

1. exp Obesity/
2. body mass index/
3. exp body weight changes/
4. exp Overweight/
5. (obes* or overweigh* or (body adj2 mass*) or (over adj2 weigh*) or overnutriti* or (over adj2 nutriti*) or hypernutriti* or hyperphagi* or (hyper adj2 nutriti*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
6. (appetite adj2 (depress* or suppress*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
7. (antiobes* or (anti adj2 obes*) or anore* or hyperphag* or hunger or hungry or satiety or satiation or (body adj2 weigh*) or (excess adj2 fat*) or (excessive adj2 fat*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
8. (weight adj2 (control* or manag* or excess or reduction* or loss* or chang* or swing*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
9. exp Metformin/
10. (metformin* or metphormin* or biguanid* or glucophage or siofor or dialon).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
11. 9 or 10
12. ((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or drug therapy.fs. or randomly.ab. or trial.ab. or groups.ab.) not (exp animals/ not humans.sh.)
13. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
14. 11 and 12 and 13
15. exp Diabetes Mellitus/ or diabetes.mp.
16. 14 not 15
17. 13 not 15

PubMed

(((((((((obesity [mesh]) OR overweight [mesh]) OR body mass index [mesh:noexp]) OR body weight changes [mesh]) OR (obes*[tw] OR overweigh*[tw] OR (body mass*[tw]) OR (over weigh*[tw]) OR overnutriti*[tw] OR (over nutriti*[tw]) OR hypernutriti*[tw] OR (hyper nutriti*[tw]) OR (appetite depress*[tw]) OR (appetite suppress*[tw]) OR antiobes*[tw] OR (anti obes*[tw]) OR anore*[tw] OR hyperphag*[tw] OR hunger[tw] OR hungry[tw] OR satiety[tw] OR satiation[tw] OR (body weigh*[tw])

OR (excess fat*[tw]) OR (excessive fat*[tw]) OR (weight control*[tw]) OR (weight manag*[tw]) OR (weight excess*[tw]) OR (weight reduction*[tw]) OR (weight loss*[tw]) OR (weight chang*[tw]) OR (weight swing*[tw])))) AND ((metformin[mesh]) OR ((metformin*[tw] OR metphormin*[tw] OR glucophage OR siofor OR dialon)))) AND (((randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR clinical trials as topic[mesh:noexp] OR randomly[tiab] OR trial[ti]) NOT (animals [mh] NOT (humans [mh] AND animals[mh])))))) NOT (Diabetes Mellitus OR diabet*)

Cochrane Library

#1 MeSH descriptor: [Obesity] explode all trees

#2 MeSH descriptor: [Body Mass Index] explode all trees

#3 MeSH descriptor: [Body Weight Changes] explode all trees

#4 MeSH descriptor: [Overweight] explode all trees

#5 obes* or overweigh* or (body near/2 mass*) or (over near/2 weigh*) or overnutriti* or (over near/2 nutriti*) or hypernutriti* or (hyper near/2 nutriti*) or (appetite near/2 (depress* or suppress*)) or antiobes* or (anti near/2 obes*) or anore* or hyperphag* or hunger or hungry or satiety or satiation or (body near/2 weigh*) or (excess near/2 fat*) or (excessive near/2 fat*) or (weight near/2 control*) or (weight near/2 manag*) or (weight near/2 excess) or (weight near/2 reduction*) or (weight near/2 loss*) or (weight near/2 chang*) or (weight near/2 swing*)

#6 #1 or #2 or #3 or #4 or #5

#7 MeSH descriptor: [Biguanides] explode all trees

#8 MeSH descriptor: [Metformin] explode all trees

#9 metformin* or metphormin* or biguanid* or glucophage or siofor or dialon or dimethylbiguanidin* or dimethylguanylguanidin*

#10 #7 or #8 or #9

#11 #6 and #10

#12 MeSH descriptor: [Diabetes Mellitus] explode all trees

#13 diabet*

#14 #12 or #13

#15 #11 not #14

Embase

('obesity'/exp OR 'body weight management'/exp OR 'weight reduction'/exp OR 'body mass'/de OR 'body weight'/de OR 'weight change'/de OR 'weight gain'/de OR obes* OR overweigh* OR (body

NEAR/2 mass*) OR (over NEAR/2 weigh*) OR overnutriti* OR (over NEAR/2 nutriti*) OR hypernutriti* OR (hyper NEAR/2 nutriti*) OR (appetite NEAR/2 (depress* OR suppress*)) OR antiobes* OR (anti NEAR/2 obes*) OR anore* OR hyperphag* OR hunger OR hungry OR satiety OR satiation OR (body NEAR/2 weigh*) OR (excess NEAR/2 fat*) OR (excessive NEAR/2 fat*) OR (weight NEAR/2 (control* OR manag* OR excess OR reduction* OR loss* OR chang* OR swing*))) NOT ('diabetes mellitus'/exp OR diabet*) AND ('metformin'/exp OR metformin* OR metphormin* OR glucophage OR siofor OR dialon OR dimethylbiguanidin* OR dimethylguanylguanidin*) AND ('crossover procedure':de OR 'double-blind procedure':de OR 'randomized controlled trial':de OR 'single-blind procedure':de OR random*:de,ab,ti OR factorial*:de,ab,ti OR crossover*:de,ab,ti OR ((cross NEXT/1 over*):de,ab,ti) OR placebo*:de,ab,ti OR ((doubl* NEAR/1 blind*):de,ab,ti) OR ((singl* NEAR/1 blind*):de,ab,ti) OR assign*:de,ab,ti OR allocat*:de,ab,ti OR volunteer*:de,ab,ti)