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ONE MINUTE CONSULT
BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

Q: Should I consider metformin therapy for weight loss in patients with obesity but without diabetes?

A: Yes. Evidence supports the weight-loss effects of metformin in adults with obesity and without type 2 diabetes. The magnitude of metformin-induced weight loss is modest but clinically significant, and it is achievable at low cost with an agent that has proven long-term safety, few serious adverse effects, and well-documented favorable nonglycemic effects. To date, metformin is the only pharmacologic weight-loss intervention to demonstrate long-term effects.[1]

Thus, in the absence of contraindications, metformin should be seriously considered as an off-label initial therapy and as an adjunct to antiobesity medications approved by the US Food and Drug Administration for the management of obesity, particularly in the presence of specific concomitant conditions, as will be discussed here.

SUPPORTING EVIDENCE

The main sources of evidence for weight loss with metformin in people without type 2 diabetes come from the Diabetes Prevention Program trial (DPP)[2] and its long-term follow-up, the Diabetes Prevention Program Outcomes Study (DPPOS).[1]

The DPP, a 3-arm randomized controlled trial, compared the effects of intensive lifestyle intervention, metformin 1,700 mg/day, and placebo in 3,234 participants with prediabetes. The primary outcome measure was prevention or delayed onset of type 2 diabetes, with weight loss reported as a secondary outcome.[2] The mean weight and body mass index (BMI) of the overall population in the study was 94.2 ± 20.3 kg and 34 ± 6.7 kg/m^2, respectively.

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During the initial 2.8-year follow-up, the metformin group experienced an average weight loss of 2.1 kg, compared with 5.6 kg in the lifestyle intervention group, and 0.1 kg in the placebo group.[2]

Weight loss is maintained

Unlike the weight loss experienced in the intensive lifestyle intervention group, weight loss in the metformin group was maintained throughout the DPP and DPPOS follow-up periods (N = 2,766 participants). Those on metformin had an average 2.5-kg weight loss over time, while the lifestyle intervention group progressively regained weight, with a final average weight loss of 2.0 kg after 10 years of follow-up.[3]

Approximately 30% of participants randomized to metformin lost more than 5% of their body weight in the first year, and a post hoc analysis demonstrated that their mean weight loss relative to baseline was 6.2% after 15 years of follow-up, compared with 3.7% in the lifestyle intervention arm. Adherence and weight loss during the first year of treatment with metformin were relevant predictors of long-term weight-loss maintenance.[1] Because the DPP and DPPOS were not designed primarily to assess weight loss, caution must be exercised when interpreting these data.

To date, the largest evaluation of weight loss with metformin as a primary outcome in patients without diabetes is the preliminary phase of the Biguanides and Prevention of the Risks in Obesity trial,[4] with 324 participants with abdominal obesity (inclusion criterion was waist-to-hip ratio, not BMI) and no diabetes. Participants were randomized to receive metformin 1,700 mg/day or placebo. After 12 months of treatment, metformin had a significantly better effect on weight

(mean −2 kg, 95% confidence interval [CI] −3.0 to −1.1, vs placebo −0.8 kg, 95% CI −1.6 to 0.1, $P < .06$).

Higher degrees of insulin resistance

A more recent nonrandomized, real-world study assessed the efficacy of metformin for weight loss in 154 patients with obesity and no diabetes compared with 45 control participants.[5] The mean weight loss in the metformin group was 5.8 kg (± 7.0), whereas controls gained 0.8 kg (± 3.5 kg) on average ($P < 0.0001$).[5] Both absolute and relative weight loss increased with higher degrees of insulin resistance, as measured by the Matsuda index and HOMA index.[5] The study provides good real-world evidence on the use of metformin in patients with obesity and no diabetes, but the control group comprised patients who chose not to use medication as a means of reducing weight. Consequently, the possibility of innate bias should be considered when interpreting the results.

A meta-analysis that included 21 trials and 1,004 participants analyzed the effect of metformin on BMI in different populations and found that in patients with obesity, BMI was reduced by 1.3 units (weighted mean difference [WMD] 1.31; 95% CI −2.07 to −0.54).[6] A subanalysis found that metformin had the most pronounced effect in the population with BMI greater than 35 kg/m^2 (WMD −1.12; 95% CI −1.84 to −0.39), at doses higher than 1,500 mg/day (WMD −1.01; 95% CI −1.29 to −0.73) for at least 6 months (WMD −1.09; 95% CI −1.71 to −0.47).[6]

Evidence regarding the timeframe in which weight loss might be expected to occur is inconsistent. Commonly, however, in trials with longer follow-up periods, weight loss generally starts after 4 weeks of treatment with metformin and occurs mainly during the first 6 to 12 months of continuing metformin therapy.[1,7,8]

SPECIFIC POPULATIONS

Prediabetes

In the DPP trial, the incidence of diabetes was 58% lower (95% CI 48% to 66%) in the lifestyle intervention group and 31% lower (95% CI 17% to 43%) in the metformin group compared with placebo.[2] However, metformin proved to be particularly effective for preventing or delaying diabetes in the subgroups of participants with higher BMI (≥ 35), younger age (< 60), and higher baseline fasting blood glucose and hemoglobin A1c, and in women with a history of gestational diabetes.[2,9,10] This particular effect has been shown to be durable after 15 years of follow-up.[9] In these populations, the role of metformin goes beyond its weight loss effects, and its use should be encouraged with the dual goal of promoting weight loss and preventing or delaying the onset of type 2 diabetes.

PATIENTS TREATED WITH ANTIPSYCHOTIC DRUGS

Most antipsychotic drugs are associated with weight gain. It has been reported that 75% of patients receiving antipsychotic agents increased their baseline weight by more than 7%. Atypical antipsychotics have greater potential for inducing weight gain, and among them, clozapine and olanzapine are the agents most associated with weight gain, followed by risperidone and quetiapine.[11] These are also the agents for which the literature on metformin's weight-attenuating and weight-loss effects is more abundant. However, there does not appear to be an antipsychotic drug-specific beneficial effect of metformin, and it is rather the magnitude of weight gain that drives metformin efficacy.

Several trials have demonstrated beneficial effects of metformin in reversing or preventing weight gain associated with antipsychotic drug therapy. A meta-analysis including 12 studies and 743 participants confirmed that metformin is effective in treatment of weight gain associated with these agents. The mean weight loss was 3.27 kg (95% CI −4.66 to −1.89; Z = 4.64; $P < .001$), and metformin resulted in significant reduction in BMI (−1.13; 95% CI −1.61 to −0.66) compared with placebo.[12]

Weight gain can be associated with other medications, including some anticonvulsants, antidepressants, and systemic glucocorticoids, but evidence regarding the utility of metformin in those groups of patients is lacking.

Polycystic ovary syndrome

In women with polycystic ovary syndrome, metformin therapy has been shown to increase ovulation, menstrual frequency, fertility, and rates of live birth. A meta-analysis comparing orlistat with metformin in women with polycystic ovary syndrome found that both had similar favorable effects on BMI, with a mean decrease in BMI of 3.4 to 4.55 with metformin, and 4.48 to 5.7 with orlistat (difference −0.65%, 95% CI −2.03 to 0.73).[13]

POTENTIAL MECHANISMS

Some evidence suggests that the mechanisms underlying metformin's effects on body weight are much broader than its insulin-sensitizing effects. Additional proposed mechanisms include the following:

- Appetite suppression through increased secretion

of glucagon-like peptide 1 and peptide YY, and increased hypothalamic leptin sensitivity
- Alteration of the gut microbiome
- Induced expression and secretion of growth-differentiating factor 15, which reduces food intake, body mass, fasting insulin, and glucose intolerance.[14,15]

Although most studies have used metformin in its immediate-release formulation, there is sufficient evidence to suggest no differences between immediate-release and extended-release formulations in terms of their weight-loss properties or the secretion of substances that potentially underlie this effect.[16]

SAFETY AND SIDE EFFECTS

When metformin is used and prescribed appropriately, serious adverse events are extremely rare. The most common side effects are gastrointestinal—diarrhea, nausea, flatulence, vomiting, and abdominal discomfort. These are less frequent with postprandial use and with extended-release than immediate-release formulations. Given the lack of prospective data on the effect of metformin on weight loss, it is unclear whether weight loss is associated with gastrointestinal side effects. Since the magnitude of weight loss during the DPP (and its maintenance during the DPPOS) was directly related to adherence to metformin therapy,[17] such an association seems unlikely.

The main contraindication associated with metformin is severe renal impairment, defined as an estimated glomerular filtration rate (eGFR) less than 30 mL/min/1.73 m^2. In patients with eGFRs between 30 and 60 mL/min/1.73 m^2, the accepted recommendation is to reduce the dose, but no specific dose adjustments or maximum doses have been validated in clinical trials.[18] If metformin is being considered as a weight-loss strategy in patients without diabetes, the following approaches are reasonable:
- eGFR less than 45 mL/min/1.73 m^2: refrain from starting metformin
- eGFR 45 to 60 mL/min/1.73 m^2: prescribe a maximum total daily dose of 1,500 mg (or 1,700 mg if prescribing an immediate-release formulation)
- eGFR 30 to 45 mL/min/1.73 m^2 and already on metformin therapy: adjust to a maximum daily dose of 1,000 mg.

Chronic metformin use has been associated with a decrease in serum vitamin B12 levels without clinical manifestations. Reported in approximately 7% of patients, it is attributed to interference with vitamin B12 absorption. It is rarely associated with anemia and appears to be reversible with discontinuation of metformin or with vitamin B12 supplementation, or both.[19]

COST

Metformin is widely available, with an average price of about $10 for a 90-day supply. There are no studies of the cost-effectiveness of metformin as a weight-loss intervention. However, cost-effectiveness analysis of metformin as a diabetes prevention strategy in the DPP concluded that, compared with placebo, it was "extremely cost-effective (that is, improved outcomes at a low incremental cost) or even cost-saving (improved outcomes and reduced total costs)."[20]

BOTTOM LINE

It is well known that a small but sustained reduction in body weight (3% to 5%) is associated with improved glucose metabolism, blood pressure, and lipids, and is a strong predictor of diabetes prevention. Available evidence supports the use of metformin as an initial and adjuvant weight-loss medication, especially in the presence of prediabetes, severe obesity (BMI ≥ 35), use of antipsychotic drugs, or polycystic ovary syndrome. It should be considered a long-term treatment, particularly in patients who demonstrate a good response. The aim is to achieve a dosage of 1,500 mg/day or more (or adjusted by renal function), leveraging extended-release formulations and slow titration.

DISCLOSURES

Dr. Pantalone has disclosed consulting for Astra Zeneca, Bayer, Corcept, Diasome, Eli Lilly, Merck, Novo Nordisk, Sanofi Aventis, Twinhealth; teaching and speaking for Astra Zeneca, Corcept, Merck, and Novo Nordisk; and research for Bayer, Eli Lilly, Merck, Novo Norkisk, and Twinhealth. Dr. Burguera has disclosed advisor or review panel participation for Novo Nordisk. The other authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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