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CME CREDIT

BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

Q: Is there a role for metformin or acarbose as a weight-loss agent in the absence of diabetes?

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A: No. Based on the evidence so far, neither metformin (Glucophage) nor acarbose (Precose) can be recommended as a weight-loss agent in nondiabetic patients, since neither drug has been shown to produce significant, consistent weight loss in this population.

Diabetic patients tend to gain weight while taking sulfonylureas, thiazolidinediones, or insulin, but not metformin or acarbose. In fact, in several studies, patients with type 2 diabetes lost weight while taking metaformin or acarbose.

These observations led some to expect that these drugs might be useful as weight-loss agents even in patients without diabetes. Several studies have directly or indirectly addressed this issue, with disappointing results.

Neither drug produces significant, consistent weight loss in nondiabetic patients

METFORMIN

Weight loss in patients with diabetes

Metformin, an insulin-sensitizing biguanide, is widely used to lower blood glucose concentrations in patients with type 2 diabetes.

Most patients with type 2 diabetes have features of insulin resistance and the metabolic syndrome: eg, abdominal obesity, low levels of high-density lipoprotein cholesterol, high levels of triglycerides, insulin, leptin, and plasminogen activator inhibitor-1 (impaired fibrinolytic activity), and hypertension. Several studies showed that metformin can improve all these features.

In addition, several studies found that patients with type 2 diabetes lost weight while taking metformin, with significant reductions in total body fat and visceral fat in those with preexisting abdominal or visceral obesity. Since visceral fat is a major contributor to insulin resistance, reduction of visceral fat may partly explain how metformin improves insulin resistance.

Metformin-induced weight loss appears to be mediated by reduction of insulin resistance, with subsequent reduction of fasting serum insulin levels. There is also some evidence that metformin may have an anorectic effect, which may be another mechanism by which it causes weight loss.[1]

Studies in nondiabetic patients

The BIGPRO trial (Biguanides and Prevention of the Risks in Obesity),[2] published in 1996, included 324 middle-aged, nondiabetic people in France with high waist-to-hip ratios, who were randomized to receive metformin or placebo and were followed for 1 year.

Metformin induced significantly greater weight loss than placebo (2 kg vs 0.8 kg), as well as significant improvements in fasting blood glucose, low-density lipoprotein (LDL) cholesterol, and insulin levels and fibrinolytic activity.

Glueck et al[3] studied 31 nondiabetic patients with severe obesity (mean body mass index 43). All of them received metformin 2,550 mg daily for 28 weeks and were advised not to change their diet or exercise regimen. They lost an average of 5.9 kg ($P < .001$) and also showed significant reductions in waist circumference, waist-to-hip ratio, calorie intake, and levels of insulin, leptin, and LDL cholesterol.

*This article discusses therapies that are not approved by the US Food and Drug Administration.

The Diabetes Prevention Program[4] included 3,234 nondiabetic people (mean body mass index 34) with elevated levels of fasting and post-load plasma glucose. Subjects were randomized to placebo, metformin 850 mg twice daily, or a lifestyle modification program and were followed for a mean of 2.8 years.

The placebo group did not lose any weight; in contrast, the metformin group lost a mean of 2 kg, which was statistically significant, but the lifestyle modification group lost even more—a mean of 4 kg. Compared with the placebo group, the incidence of diabetes during the follow-up was 31% lower in the metformin group and 58% lower in the lifestyle modification group.

Metformin in nondiabetic patients: Weight loss is modest at best

In most studies of metformin in people without diabetes, the subjects were obese and had various features of insulin resistance or polycystic ovary syndrome.

In most of these studies, taking metformin led to a loss of weight and improvements in insulin resistance and the metabolic syndrome. However, a few studies did not show any statistically significant weight loss, and in the rest the mean weight loss was only modestly greater with metformin than with placebo (2–3 kg).

Studies in patients who were not obese showed no significant weight loss.

ACARBOSE

Weight loss in patients with diabetes

Acarbose lowers blood glucose levels by inhibiting alpha-glucosidases in the gastrointestinal tract, thereby delaying the hydrolysis of ingested disaccharides and complex carbohydrates and resulting in a dose-dependent reduction in the postprandial rise in blood glucose.

In contrast to sulfonylureas, thiazolidinediones, and insulin, acarbose has been reported to result in slight weight loss (0.3 to 1 kg). In addition, though the results are not consistent, some studies with acarbose have reported improvements in elevated insulin and lipid levels.

Acarbose does not seem to have a significant effect on nutrient intake. Any weight loss may be due to inhibition of carbohydrate digestion and delayed gastric emptying. An exaggerated and sustained postprandial release of glucagon-like peptide-1 from the intestine in response to acarbose may be partly responsible for these effects.[5]

Studies in nondiabetic subjects

Bayraktar et al[6] studied 50 obese women (mean body mass index 36) who were put on a low-calorie diet for 12 weeks; 25 of them also received acarbose during those 12 weeks while the rest received no additional treatment. Those who received acarbose lost a mean of 6.1 kg, compared with 4.5 kg with diet alone; the difference was not significant. Similarly, there were no significant differences in changes in insulin, LDL cholesterol, or triglyceride levels between the two groups.

Hauner et al[7] studied 110 obese people (body mass index 32 to 38). After 10 to 16 weeks on a very-low-calorie diet, they were randomized to receive either acarbose or placebo for 26 weeks. The acarbose group had no further change in weight, whereas the placebo group gained back 0.6 kg; the difference was not statistically significant.

Acarbose in nondiabetic patients: No meaningful weight loss

Even though acarbose caused consistent weight loss in a dose-dependent fashion in studies in animals, results in nondiabetic people have not been encouraging.

NO REASON TO USE METFORMIN OR ACARBOSE FOR WEIGHT LOSS ALONE

Metformin clearly causes a modest weight loss in obese people with or without diabetes. The weight loss is associated with improvements in measures of insulin resistance and the metabolic syndrome. In addition, the Diabetes Prevention Program showed that metformin may prevent diabetes.

Although metformin has an emerging role in people without diabetes who have features of insulin resistance or polycystic ovary syndrome, it can not be recommended for routine weight loss in these patients: the amount of weight loss is too small, and its role in patients who do not have insulin resistance is not clear.

Metformin may have a role in metabolic syndrome, but not in weight loss

Acarbose has been shown to result in slight weight loss in diabetic patients and may also cause some improvement in measures of the metabolic syndrome, possibly as a result of weight loss or improvement in glycemic control. On the other hand, in nondiabetic obese patients it appears neither to promote weight loss to a significant degree nor to help patients keep weight off after successful weight loss using other methods.

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