

# Metformin Induced Anorexia and Weight Loss

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## Abstract

*The clinical findings in three elderly patients with Type 2 diabetes treated with metformin are presented. Three patients with Type 2 diabetes mellitus presented for endocrine consultation after extensive evaluation for severe weight loss. No occult malignancy was found. The appetite returned and weight gradually increased with discontinuation of metformin. Simple discontinuation of metformin may circumvent unnecessary and extensive diagnostic evaluation for severe weight loss in elderly patients with Type 2 diabetes mellitus.*

## Introduction

Metformin is a biguanide that was re-introduced in the United States in 1995 to treat patients with Type 2 diabetes mellitus. It effectively results in reductions in fasting and postprandial blood glucose concentrations and glycosylated hemoglobin levels, primarily by decreasing hepatic glucose production.<sup>1,2</sup> In addition, metformin acts to lower blood glucose concentrations by improving insulin sensitivity and decreasing intestinal absorption of glucose. The drug may offer other potential benefits, such as producing weight loss or minimizing weight gain in obese patients.

Its most common side effects are gastrointestinal such as diarrhea, dyspepsia, nausea and anorexia. Lactic acidosis may also occur, but it is rare if metformin is avoided in patients with contraindications to its use. Therefore, metformin is contraindicated in patients with renal insufficiency (patients with serum creatinine  $\geq 1.5$  mg/dL (males),  $\geq 1.4$  mg/dL (females) or abnormal creatinine clearance), congestive heart failure requiring pharmacologic therapy and acute or chronic metabolic acidosis. Hypoglycemia does not occur under usual circumstances, but could occur when caloric intake is deficient or during concomitant use with other glucose lowering agents. Elderly, debilitated or malnourished patients, and those with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycemic effects.<sup>3</sup>

Metformin-induced weight loss is found to be a desirable effect in obese patients with Type 2 diabetes mellitus. However, excessive weight loss in elderly patients with Type 2 diabetes mellitus may be underreported and unrecognized. We report three cases of metformin induced weight loss and anorexia that prompted evaluation for occult malignancy. In each case, anorexia and weight loss were reversed with the discontinuation of metformin.

## Case #1

An 80 year-old Chinese female was diagnosed with Type 2 diabetes mellitus eight years prior to presentation. She was placed on metformin 500 mg daily and glipizide 5 mg daily two years later. She presented with marked anorexia and a ten pound weight loss over six months (106 to 96 lb). She denied early satiety, but complained of an inability to appreciate tasty foods. On exam, she weighed 96 pounds with a height of 5'1.5" (BMI=18). She underwent extensive gastrointestinal evaluation to exclude a visceral malignancy. An abdominal CT revealed fatty infiltration of the liver and no other abnormalities. An upper GI series with small bowel follow through as well as a malabsorption evaluation were unrevealing. Thyroid function studies were normal. She was referred for endocrine consultation. Metformin was discontinued, and her appetite was restored to normal within one month. She regained nine pounds five months after discontinuation of metformin.

## Case #2

A 79 year-old Chinese female with Type 2 diabetes mellitus on metformin 1000 mg twice daily presented with a 42 pound weight loss (128 to 86 lb) over two years. She complained of anorexia, but denied nausea, vomiting or diarrhea. On exam, she weighed 86 pounds and measured 5'2.5" in height (BMI=15.7). An esophagogastrosocopy demonstrated no gastric malignancy. At that time, her glycosylated hemoglobin was 6.6% and TSH level normal at 0.95 uU/mL (0.24-3.80). She was referred for endocrine evaluation. Metformin was discontinued, and her weight increased to 99 pounds seven months later. However, her glycosylated hemoglobin also increased to 8.1%, so she was started on glimepiride 0.5 mg qd.

## Case #3

A 70 year-old Japanese male with Parkinson's disease was diagnosed with Type 2 diabetes mellitus five years prior to presentation and started on metformin 500 mg twice daily. Glipizide 20 mg daily was added two months prior to presentation. He presented with anorexia, generalized weakness and a progressive 44 pound weight loss (190 to 146 lb) over five years. He was hospitalized for five days to exclude a gastrointestinal malignancy. Abdominal CT scan was unremarkable, and upper endoscopy only revealed mild gastritis. Colonoscopy demonstrated diverticuli and small polyps. His TSH level was normal at 1.26 uU/mL (0.24-3.80). On exam, he weighed 146 lbs and measured 5'7" in height (BMI=23). His metformin was discontinued, and his appetite returned. He subsequently regained 20 pounds in one year. Fifteen months after discontinuation of metformin, he weighed 169 pounds. However, one year later his

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course was complicated by aspiration pneumonia. He currently requires tube feeding, and his weight is 143 pounds.

## Discussion

Metformin-induced weight loss in obese subjects is well documented. In the 1965, Pedersen et al. studied seven hospitalized obese women and found a 20% greater average weight reduction during periods in which metformin was given in addition to dietary caloric restriction.<sup>4</sup> More recently, most studies show a modest weight loss between 2-3 kg during the first year of treatment with metformin. This effect has been observed in non-diabetic<sup>5</sup> and diabetic<sup>1,6</sup> obese subjects. 324 obese subjects were randomized to metformin or placebo for one year, and compared with placebo, metformin induced a significant weight loss (2.0 kg vs. 0.8 kg).<sup>7</sup> A study of obese women on caloric restricted diets with and without polycystic ovarian syndrome randomized to metformin 850 mg bid or placebo showed that after six months, metformin reduced body weight and body mass index to a significantly greater degree than placebo.<sup>8</sup>

In 1995, Stumvoll et al. studied obese Type 2 diabetic subjects and found that metformin 2550 mg daily for 12 weeks produced a 3 kg weight loss. This weight loss was largely accounted for by loss of adipose tissue.<sup>1</sup> The mechanism for weight loss is uncertain, but it is proposed that increased thermogenic activity of brown adipose tissue and reduction in adipose mass or increased "futile" cycling of substrates are two possibilities.<sup>9</sup> In addition, studies of obese women with Type 2 diabetes mellitus indicate that metformin may induce appetite suppression as demonstrated by significantly lower hunger ratings on metformin compared to placebo. Caloric intake appeared to decrease with metformin in a dose dependent manner.<sup>6</sup>

Although modest weight loss secondary to metformin in obese subjects is well known, in our review of the literature there is an absence of documented severe weight loss induced by metformin sufficient to raise suspicion of an occult malignancy. We believe this phenomenon is unrecognized or underreported by physicians. The first two patients we report here

were of normal weight prior to the administration of metformin. The third patient reported was obese prior to the administration of metformin with a BMI of 30. All three were elderly Asian patients. We suspect that the anorectic effect in addition to the "metallic taste" that may occur with metformin therapy resulted in considerably decreased caloric intake. Clinicians should be aware of the potential anorectic effect of metformin, which may mimic cachexia of malignancy, especially in the elderly patient. This awareness may circumvent needless evaluation for occult malignancy. Patients with type 2 diabetes who are taking metformin and experience severe weight loss, anorexia and cachexia deserve a drug-free interval before undergoing extensive diagnostic testing.

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