A Common Drug Causing a Common Side Effect at an Uncommon Time: Metformin-Induced Chronic Diarrhea and Weight Loss After Years of Treatment

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Background

Type 2 diabetes is a common condition, with a worldwide prevalence of 9.3% as of 2019 (1). Metformin is the most common drug used and is the first-line agent in type 2 diabetes management. It is also considered one of the safest pharmacological agents for the treatment of the disease. However, gastrointestinal side effects are common, occurring in up to 75% of those who take metformin (2). These side effects may include diarrhea, nausea, vomiting, abdominal discomfort, and/or flatulence, with severity ranging from mild to severe. These complications are more common with immediate-release preparations of metformin than with its extended-release formulation. Discontinuation and nonadherence rates have been as high as 46% with metformin because of these issues (3).

But still, metformin remains the first choice of medication for many insulin resistance syndromes because of its effect on weight. In the Diabetes Prevention Program research study (4), metformin reduced weight by a mean 2.9 kg, and this effect persisted up to 8 years. Metformin-associated weight loss begins with initiation of the medication and is beneficial in obese individuals with or without diabetes. However, weight loss can become an unintended adverse side effect in lean individuals with type 2 diabetes.

We report here a case series of patients with both adverse side effects—diarrhea and weight loss—that began after long-term use of metformin (Table 1) and provide a review of the related literature.

Case Presentations

Case 1

A 63-year-old woman known to have diabetes for 17 years with fair glycemic control presented with unintentional weight loss of 10 kg in the past year. She complained of intermittent, self-resolving, painless, small-volume, watery diarrhea and progressive dyspepsia for the same duration. She had a good appetite and healthy lifestyle. She was evaluated by a primary care physician, gastroenterologist, and psychiatrist for the above complaints and was referred as having diabetic diarrhea.

On evaluation, she was normotensive, with a BMI of 23.5 kg/m^2. She had no lymphadenopathy, and review of systems was unremarkable except for distal sensorimotor neuropathy in the lower limbs. Because of a concern of autonomic neuropathy, she was evaluated. Her electrocardiogram showed a sinus rhythm, there was no postural drop in blood pressure, and heart rate variability with deep breathing was normal.

A trial of metformin withdrawal was initiated. Within 1 week, she got better. At her last follow-up, she had gained weight, the diarrhea had stopped, and the dyspepsia had reduced. She was not achieving glycemic control with increasing doses of a sulfonylurea or a sodium–glucose cotransporter 2 (SGLT2) inhibitor and so was switched to a coformulation of insulin degludec and insulin aspart.

Case 2

A 74-year-old woman with longstanding diabetes presented for management of type 2 diabetes. She had been having episodes of food-induced, mild, watery, solid, and unformed diarrhea with fecal incontinence for 1.5 years. She was evaluated thoroughly by a gastroenterologist, diagnosed with irritable bowel syndrome, and prescribed an antidepressant for its treatment.

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TABLE 1 Detailed Characteristics of Patients in Cases 1–3

	Age, years/ Sex	Diabetes Duration at Onset of Symptoms, years	Symptoms	Medications at Onset of Symptoms	Weight, kg/BMI, kg/m^2)	Mean A1C During Symptoms, %	Complications	Tests	Endoscopy	Time to Symptom Resolution After Stopping Metformin	Follow-Up Duration, months/ Weight Status	Medications After Metformin Discontinuation
Case 1	63/ Female	17	Weight loss of 10 kg, recurrent painless diarrhea, dyspepsia for 1 year	Vildagliptin 100 mg/day, metformin XR 2 g/day, glimepride 0.5 mg/day, chlorthalidone 12.5 mg/day, rosuvastatin 5 mg/day	58/23.5	6.8	Mild retinopathy, no albuminuria; both AJ absent; SW test absent sensation	TSH 3.2 mIU/ L; stool examination normal; stool culture negative; chest radiography normal; HIV negative	Upper GI with duodenum biopsy normal; colonoscopy normal	1 week	12/gained 6 kg	Vildagliptin 100 mg/day, $I_{Deg/Asp}$ 0.5 units/kg
Case 2	74/ Female	18	Painless postprandial diarrhea with fecal incontinence, dyspepsia for 1.5 years	Metformin SR 1.5 g/day, teneligliptin 20 mg/day, clopidogrel 75 mg/day, nebivolol 5 mg/ day, calcium carbonate 500 mg/day, alprazolam 0.5 mg/day	65.4/ 21.5	6.4	No retinopathy, microalbuminuria; both AJ absent; SW test sensation present	TSH 4.5 mIU/ L; CEA normal; CT abdomen no abnormality; stool examination normal	Colonoscopy normal	5 days	6/gained 4.4 kg	Glimepride 0.5 mg/day, teneligliptin 20 mg/day
Case 3	60/ Male	24	Weight loss of 8 kg in 8 months	Glimepride 2 mg/day, metformin SR 2 g/day, teneligliptin 20 mg/day, glargine insulin 16 units/day	63.6/ 23.1	7.5	No retinopathy, microalbuminuria; both AJ absent; SW test absent sensation	TSH 5.1 mIU/ L; MRI abdomen normal; chest radiography normal; HIV negative; FDG PET negative	Upper GI endoscopy normal	1 week	6/gained 3 kg	Glimepride 4 mg/ day, basal-bolus insulin 0.4 units/ kg

AJ, ankle jerk; CEA, carcinoembryonic antigen; CT, computed tomography; FDG PET, fluorodeoxyglucose positron emission tomography; GI, gastrointestinal; $I_{Deg/Asp}$, degludec/aspart insulin coformulation; SR, sustained release; SW, Semmes-Weinstein monofilament; TSH, thyroid-stimulating hormone; XR, extended release.

On examination, she was lean and normotensive and had no features of malabsorption. Her autonomic function tests were normal, as was her anal tone. It was recommended that she withhold metformin for a few weeks. A small dose of sulfonylurea was added in its place. She showed dramatic improvement in her diarrhea and had gained weight when seen at her last visit.

Case 3

A 60-year-old man who was a nonsmoker with long-standing diabetes, was concerned about progressive, unintentional weight loss without any constitutional symptoms despite adequate caloric intake. He was evaluated by a gastroenterologist for this complaint, but no reason could be found.

On examination, he was afebrile and had no lymphadenopathy or organomegaly. He was started on a trial of withholding metformin, and after a few weeks, he started showing improvement. By the time of his last visit, he had gained ~3 kg.

Questions

1. What are the reasons for insidious-onset diarrhea and weight loss in otherwise normal patients with type 2 diabetes?
2. How does metformin cause diarrhea and weight loss in people with type 2 diabetes?
3. What is the etiology of metformin-induced, late-onset diarrhea and weight loss?
4. Why is it important to recognize this entity?

Commentary

Chronic diarrhea can occur in people with type 2 diabetes because of numerous reasons including medications (i.e., metformin, α-glucosidase inhibitors, and glucagon-like peptide 1 [GLP-1] receptor agonists), coexistent endocrine disorders, autonomic dysfunction, celiac disease, pancreatic insufficiency, or bacterial overgrowth syndrome, in addition to traditional differentials. Unintentional weight loss in type 2 diabetes can occur, apart from systemic causes, as a result of uncontrolled diabetes per se, medications (i.e., metformin, SGLT2 inhibitors, and GLP-1 receptor agonists), autoimmune thyroid or adrenal disorders, depression, coexistent unrecognized systemic infection, or autonomic diarrhea.

Metformin-induced diarrhea developing in individuals starting the medication has been attributed to changes in the gut microbiome, increased intestinal glucose and bile acid turnover, and increasing GLP-1 concentration (3). The diarrhea usually reduces with time or after dose reduction, which may be followed by gradual up-titration. Metformin-induced weight loss has been hypothesized to result from appetite-modulating effects in central nervous system, reduction in leptin production from adipose tissues, reduced carbohydrate absorption from the gut, and increased GLP-1 levels (5). Both of these side effects most commonly occur either immediately after the introduction of the drug or after a delay of a few weeks. However, the patients in all three cases presented here were on stable doses of metformin for several years before these effects developed.

Case reports of late-onset diarrhea in type 2 diabetes and in those with stable doses of metformin therapy for several years are scarce (6,7). In one report, there was no obvious precipitant factor, whereas in the other, polypharmacy with ranitidine and digoxin and nephropathy were attributed to increased metformin levels causing diarrhea.

In our case series, there were no obvious precipitating factors such as autonomic neuropathy or drug interactions causing increased levels of metformin and renal dysfunction. Recently, epigenetic factors causing metformin intolerance in drug-naive patients were identified (8). With age, even the gut microbiota changes dramatically, but its role in causing diarrhea has not been studied.

As detailed in Table 1, all three of these patients underwent unnecessary biochemical testing, imaging, and endoscopy studies. Additionally, all had suffered mental anguish of worrying about potentially having a serious and life-threatening illness. Hence, educating treating physicians about this condition could reduce both patient stress and health care costs.

In conclusion, chronic diarrhea/weight loss can occur in patients with type 2 diabetes after taking stable doses of metformin for several years without any problem. This complication must be recognized early to save patients from unnecessary invasive investigations and psychological distress.

Clinical Pearls

- In patients with type 2 diabetes who take metformin, chronic diarrhea and weight loss may ensue at any time—even after several years of stable dosing.
- Probable precipitating factors might be nephropathy or drugs increasing metformin levels.
- Withholding metformin may be the first prudent step before subjecting patients to detailed, invasive, and expensive investigations.

DUALITY OF INTEREST

No potential conflicts of interest relevant to this article were reported.

AUTHOR CONTRIBUTIONS

Each of the authors contributed a case for this series, collected the necessary patient data, and drafted the manuscript. K.S. edited the manuscript and discussion. K.S. is the guarantor of this work and takes responsibility for its integrity.

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