

# Late-Onset Chronic Severe Painless Diarrhea Secondary to Metformin: Case Report and Literature Review

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## Abstract

We present a case of late-onset chronic severe painless diarrhea in an 80-year-old man with type 2 diabetes who was on metformin for 5 years. He underwent multiple laboratory and imaging investigations with no underlying cause found. After detailed medication review, a trial of metformin discontinuation resulted in immediate resolution of symptoms. This case highlights the importance of considering metformin as a cause of new-onset diarrhea in patients even if they had previously tolerated the drug well for years, as its discontinuation can potentially prevent patient inconvenience and discomfort associated with unnecessary investigations.

**Keywords:** Metformin; Diarrhea; Late-onset

## Introduction

Metformin is a biguanide antihyperglycemic agent that is currently recommended as the initial agent in most patients with type 2 diabetes, based on its efficacy in lowering blood glucose, known long-term safety, and negligible risk of hypoglycaemia or weight gain [1]. It is generally well tolerated, though it is well known to be associated with gastrointestinal side effects (i.e. diarrhea, abdominal pain, and nausea) that usually occur at initiation of therapy. However, less commonly, metformin may cause late-onset diarrhea in patients who previously tolerated it well. Thus, it is important to recognize metformin as a cause of late-onset diarrhea to potentially avoid patient discomfort and inconvenience and unnecessary investigations.

## Case Report

An 80-year-old man with a 5-year history of type 2 diabetes

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was seen in follow-up for proteinuric diabetic nephropathy. Incidentally, he reported an 8-month history of chronic painless diarrhea, with 6 - 8 explosive loose bowel movements per day associated with a 4.8 kg weight loss. Due to the frequency of episodes, his ability to leave the house was impaired. His primary care provider had arranged for multiple investigations for the diarrhea but no cause was yet identified.

His diabetes was fairly well controlled on three antihyperglycemic agents (metformin 1 g bid, gliclazide MR 30 mg daily and sitagliptin 100 mg daily), and he reported tolerating these well for several years. He had no known history of diabetic autonomic neuropathy, celiac disease or lactose intolerance. He denied the use of any laxatives, dietary supplements, herbals or artificial sweeteners. Other past history included hypertension, coronary artery disease with prior myocardial infarction, atrial fibrillation, bicuspid aortic valve repair, rheumatoid arthritis, and benign prostatic hypertrophy.

Other medications included warfarin, atorvastatin, amlodipine, doxazosin, ramipril, indapamide, potassium chloride, metoprolol, digoxin, methotrexate, pregabalin, risedronate, dutasteride, ranitidine, salbutamol, folic acid, vitamin B12, vitamin D and calcium.

Screening laboratory tests showed: creatinine 84 µmol/L, estimated glomerular filtration rate 76 mL/min, urine albumin creatinine ratio 30, sodium 135 mmol/L, potassium 4.1 mmol/L, bicarbonate 32 mmol/L, albumin 40 g/L, hemoglobin 138, and glycated hemoglobin 8.1%. Thyroid function was normal, and stools for occult blood, ova and parasites, *Salmonella*, *Shigella*, *Clostridium difficile*, enteropathic *E. coli* and *Yersinia* were all negative. Abdominal ultrasound was unremarkable. Prior to colonoscopy, he was prescribed bisacodyl and polyethylene glycol for bowel preparation, and colonoscopy revealed no major pathology apart from polyps.

On subsequent visit, due to persistence of diarrhea, a more detailed medication review was done and it was discovered that prior to onset of diarrhea, his metformin had been increased from 500 mg bid to 1 g bid, though it was also noted that in the past he had tolerated a total daily dose of metformin of 1.5 g daily without issue. In the absence of any other cause of diarrhea, he was asked to try discontinuing the metformin, and this resulted in an immediate complete resolution of diarrhea, he described it was as if "a tap had been turned off". Currently, he remains off the metformin, his weight loss has stabilized, and he has not had any recurrence of diarrhea.

## Discussion

Although gastrointestinal side effects due to metformin are

well known, metformin as a cause of chronic severe diarrhea may not be well-recognized, especially when presenting late in the course of therapy. To our knowledge, only five prior reports describe late-onset diarrhea due to metformin [2-6].

The pathophysiology of diarrhea due to metformin is not known. Potential mechanisms include increased intestinal motility and malabsorption from decreased ileal bile salt re-absorption leading to an enhanced secretory effect of bile salts in the colon [7, 8] and changes in gut peptide hormone levels, including glucagon-like peptide-1 [8]. If severe, metformin-associated diarrhea may be associated with multiple electrolyte imbalances [9]. It is not clear why diarrhea due to metformin may present late in the course of therapy as opposed to at initiation.

The elderly may be at higher risk of metformin-induced diarrhea, both at initiation of treatment and later onset, due to polypharmacy and the potential for drug interactions leading to increased metformin concentrations. In our case, the patient was also on digoxin and ranitidine; both may cause elevated plasma metformin levels [10] and thus polypharmacy may have been a contributory factor. As well, the metformin dose was increased in our patient prior to development of symptoms, and this may also have played a role.

## Conclusions

In a patient who previously tolerated metformin well, new-onset metformin-associated diarrhea, if unrecognized, may lead to unnecessary investigations, additional drug therapy (i.e. anti-diarrheal agents), patient discomfort and inconvenience. Therefore, clinicians involved in the care of patients with type 2 diabetes should be aware of the potential for late-onset diarrhea due to metformin, and consider a trial of metformin discontinuation if no other causes for the diarrhea are apparent.

## Conflicts of Interest

The authors declare no relevant conflicts of interest.

## Author Contributions

All authors made substantial contributions towards the draft and final versions of the manuscript, and all gave final approval of the version to be published.

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