

Diarrhea and Metformin in a Diabetic Clinic

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In a questionnaire-based survey of 285 randomly selected diabetic patients, diarrhea was found to occur in 8%; this was found to be similar to that in 150 nondiabetic control patients attending other medical clinics (8%). When the diabetic patients were divided into separate therapeutic groups, metformin-treated (with or without sulfonylureas) patients had a markedly greater prevalence of diarrhea (20%) than those not on this drug (6%). A majority of patients with metformin-associated diarrhea had soiling of clothes as a problem, while at least two complained of frank loss of control over their anal sphincter. These patients did not have autonomic neuropathy, and in all who stopped this drug, diarrhea settled within 2–5 days. Only 6% of insulin-dependent diabetic individuals (IDD) had diarrhea, one of whom had explosive nocturnal stools with incontinence and features diagnostic of autonomic neuropathy. Metformin is by far the commonest cause of diarrhea and incontinence in our diabetic clinic, where it is used routinely. In contrast, diarrhea due to autonomic neuropathy is rare. *DIABETES CARE* 6: 472–474, SEPTEMBER–OCTOBER 1983.

Disturbances in bowel habit are quite frequent in diabetes mellitus: both constipation and diarrhea are known to occur in association with this condition.¹ Although diarrhea as a complication of diabetes was first described in 1936,² its prevalence in diabetic patients is not known. Furthermore, there is a widespread belief that diarrhea mainly occurs in insulin-dependent diabetic individuals who may have autonomic neuropathy. We have observed that diarrhea often occurs in non-insulin-dependent diabetic individuals, particularly as a complication of biguanide therapy. We undertook this survey to determine (1) the prevalence of diarrhea in a diabetic clinic population and (2) the contribution of biguanide therapy to the presence of this complication.

PATIENTS AND METHODS

A questionnaire was distributed to 300 consecutive patients attending the diabetic clinic at the Royal Free Hospital. The 16 questions posed related to their drug therapy, duration of diabetes, and their symptoms pertaining to diabetes and its complications. They were organized in a sequence that would not make the patients focus on their bowel habits alone. Patients were encouraged by the nursing staff to complete the questionnaire while waiting to see the doctor. This en-

sured the large positive response (95%) to the questionnaire. Some patients took the questionnaire home for various reasons, and either mailed it or brought it back on their next visit. The patients who answered the questionnaire (N = 285) were divided into five therapeutic groups: (1) insulin-dependent diabetic individuals (IDD), (2) sulfonylurea, (3) metformin, (4) sulfonylurea and metformin, and (5) diet.

Case notes of patients who answered yes to the question "Do you suffer from diarrhea?" were examined for further details regarding the quality of control of diabetes, previous alteration of bowel habits, features of malabsorption, and the presence of somatic and autonomic neuropathy. The presence of clinical autonomic neuropathy was assessed by the presence of postural hypotension, gustatory sweating, impotence in the male, and absence of characteristic changes in heart rate after a Valsalva maneuver. In our experience, all patients with significant established autonomic neuropathy also have concomitant somatic neuropathy and absent ankle reflexes.

For the purpose of this investigation, diarrhea was defined as unformed stools, with a frequency of bowel motions of two or more daily. It is entirely fortuitous that none of the patients included in this study was on phenformin. We do not prescribe this drug to any new diabetic individuals attending our clinic. However, we did not actively exclude any patients

TABLE 1
The prevalence of diarrhea as a symptom in various therapeutic groups*

Treatment	Total N	No. with diarrhea
1. Insulin	78	5 (6%)
2. Sulfonylureas	53	3 (6%)
3. Metformin	54	11 (20%)†
4. Sulfonylureas and metformin	45	9 (20%)†
5. Diet	35	2 (6%)

*Controls: total 150; no. with diarrhea, 12 (8%).

†P < 0.01 when compared with groups 1, 2, and 5 singly. P < 0.001 when groups 3 and 4 are collectively compared with 1, 2, and 5 together.

from our study because of phenformin intake, or indeed for any other reason.

In order to obtain a control clinic-attending population, similar questionnaires were distributed to 150 patients attending other medical clinics in the hospital. Patients attending gastroenterology clinics were naturally excluded. The format of the questionnaires handed to these "controls" was identical to that given to the diabetic patients, except for the questions specifically related to diabetes. Diabetic individuals were excluded from this population.

Statistical analysis of the various treatment groups was carried out using X^2 test with Yates' correction.

RESULTS

Diarrhea in controls. In the control population studied, diarrhea occurred in 12 of 150 patients (8%).

Bowel symptoms in diabetic patients. Two hundred eighty-five of the 300 patients (95%) given the questionnaire answered it. Forty-three patients (15%) had bowel symptoms: 24 had diarrhea and 13 had constipation, while 6 had alternating diarrhea and constipation. Thus, a total of 30 patients (10%) had diarrhea as a problem. Two of these 30 patients were on antidiarrheal medication.

The prevalence of diarrhea was the greatest in patients treated with metformin alone (20%) or in combinations with sulfonylurea (20%). Diarrhea as a symptom was present in approximately 6% of patients in each of the remaining three treatment groups. This difference between patients on metformin alone or metformin and sulfonylurea and the rest was highly significant ($P < 0.001$) (see Table 1). The prevalence of diarrhea among diabetic patients not on metformin was

similar to that observed in the control clinic-attending population.

Pattern and type of diarrhea in diabetic patients. Of the 30 patients who had diarrhea, 4 had more than 3 bowel motions, 6 had 3, and 20 had 2 bowel motions/day (see Table 2). Thirteen patients reported having more than two bouts of severe diarrhea per year, in addition to their continuous loose motions. Seven patients had loose motions at night (1 of 20 metformin-treated patients had nocturnal motions versus 6 of 10 from the rest, $P < 0.02$). Ten had watery stools: 9 of 10 metformin-treated patients versus 1 of 10 from the rest ($P < 0.05$). Thirteen patients soiled their clothes: 12 of 20 metformin-treated patients versus 1 of 10 from the rest ($P < 0.02$). Four patients complained of passing pale and bulky stools (none of these patients was on metformin); of these 4, 2 had IDDM and one had known pancreatitis. The tendency to diarrhea in the metformin-treated group was not dose related, since the few patients on 1.5 g metformin daily did not have either a greater prevalence or a greater severity of diarrhea than those on smaller doses.

A majority of the patients who had diarrhea had not reported the symptom to the doctors in the clinics, and had accepted it either as a part of the diabetic state, or as a side effect of their treatment.

In the 12 patients in this series with metformin-induced diarrhea who were asked to stop this drug, their symptoms disappeared within 2–5 days. All 12, including those who had only two bowel motions per day, reported that their bowel habits had altered since the institution of metformin therapy. In 4 of these 12 patients, the frequency of bowel motions diminished to 3 per week, a rate which was similar to that before the commencement of metformin therapy. Two patients with metformin-induced diarrhea gave a history of loose motions within 2 h of ingestion of the drug, even at a dose of 50 mg twice daily. In contrast, several patients on a total of 3 g metformin daily had no bowel symptoms.

CASE HISTORY

In order to highlight metformin-induced diarrhea, it would be relevant to state the case history of a 62-yr-old obese woman, whose diabetes was controlled with 44 IU of insulin daily. In view of the fact that she was keen to return to treatment with oral hypoglycemic agents, she was started on glibenclamide and metformin (1.5 mg) daily in place of insulin. Soon after this substitution, she started having diar-

TABLE 2
Characteristics of diarrhea in each therapeutic group

	3 motions/day	Watery motions	Pale bulky stools	Clothes soiled	Nocturnal motions
1. Insulin (N = 5)	2	2	2	1	3
2. Sulfonylureas (N = 3)	0	0	1	0	2
3. Metformin (N = 11)	4	6	0	7	1
4. Sulfonylureas and metformin (N = 9)	4	3	0	5	0
5. Diet (N = 2)	0	0	1	0	1

rhea: sudden and explosive with watery stools. Fecal incontinence followed, and she had to change 5–6 times each day. This led to considerable social embarrassment and to intense clinical investigation, including a barium meal and follow-through examination, two barium enemas, two sigmoidoscopies, and a colonoscopy. Symptomatic treatment with antidiarrheal drugs did not help. The patient attempted suicide with an overdose of drugs, and was brought to the hospital casualty department. It was only 1 mo after her discharge from the hospital following her suicide attempt that it became apparent that metformin might have been responsible for her diarrhea. Within 3 days of stopping metformin, her diarrhea disappeared.

DISCUSSION

It is clear from the data presented that diarrhea is not uncommon (8%) in diabetic patients, and that it occurs at a frequency similar to that observed in the control patient population. By far the greatest proportion of patients with diarrhea were either on metformin alone, or on metformin in combination with sulfonylureas; conversely, as many as 20% of patients on metformin had diarrhea as a symptom.

It is of interest that the prevalence of diarrhea in patients on metformin alone was identical to that of patients on metformin and sulfonylureas, and that the patients on insulin, sulfonylureas alone, or diet alone had a prevalence of 6%. This frequency is again not different to that seen in our nondiabetic controls (8%), or in those observed in another series that examined the prevalence of diarrhea without cause in a clinic-attending population in the United Kingdom.³ It thus follows that metformin in our clinic was by far the most important cause of diarrhea. Only one of the five patients with diarrhea in the IDD group had nocturnal diarrhea, absent ankle reflexes, and postural hypotension. This patient also had watery stools. This is the only patient who would fit the classical description of diarrhea due to autonomic neuropathy.

The features of metformin-induced diarrhea are watery stools, often explosive and frequently associated with soiling of clothes and incontinence. The consistent association of incontinence with diarrhea and the disappearance of both after the cessation of metformin therapy indicate a causal relationship between the diarrhea and incontinence. Hypermobility of the bowel may thus lead to a loss of sphincter tone. A similar close association between diarrhea and incontinence was observed in a recent study on incontinence in diabetic patients with autonomic neuropathy.⁴ Metformin-associated diarrhea usually occurs during the daytime and is not associated with bulky pale stools; it is also readily re-

versible. We were surprised that diarrhea in metformin-taking patients was not related to the dose of metformin: the frequency or severity of diarrhea in patients taking more than 1.5 g metformin daily was not greater than that observed in patients taking smaller doses.

The mechanism underlying diarrhea in patients taking metformin is not entirely clear. Increased intestinal motility is one possible mechanism. There are, however, no previous data showing the effect of this drug on intestinal motility. It is also possible that impaired absorption associated with these drugs may contribute to diarrhea;⁵ however, the stools of metformin-treated patients were never pale and/or bulky.

In conclusion, our study shows that the commonest cause of diarrhea and incontinence in a diabetic clinic is metformin therapy if this drug is used routinely. The first step in the investigation and management of any diabetic patient with diarrhea must hence be an inquiry into whether the patient is on metformin (or other biguanide, e.g., phenformin) before any cumbersome investigations are undertaken and other drugs prescribed for symptomatic relief of diarrhea. Further investigation is necessary to establish the mechanism underlying the pathogenesis of diarrhea and incontinence associated with this drug.

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