Altered bile in diabetic diarrhoea

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Summary and conclusions

The size and composition of the bile-salt pools in a group of diabetics with neuropathy but no diarrhoea and a group with "diabetic diarrhoea" were compared with those in a group of stable, uncomplicated diabetics. The diabetics with neuropathy had significantly more dihydroxy bile salts, a larger bile-salt pool, and a higher faecal excretion of bile than the controls. The diabetics with diarrhoea had significantly more dihydroxy bile salts, a higher glycine to taurine ratio, a smaller bile-salt pool, and increased excretions of ^{14}C-tracer and total bile salts.

We conclude that considerable alterations occur in the bile of diabetics with neuropathy or diarrhoea, and we suggest that in some cases at least these abnormalities may indicate a mechanism for diabetic diarrhoea.

Introduction

The syndrome of "diabetic diarrhoea" was first described in 1936,[1] but the underlying mechanism is still unknown. Autonomic neuropathy is a common finding in these patients[2-4] and in most cases appears to be a precursor to the development of the syndrome. Clinical improvement with antibiotics occurs,[2 5 6] and results of ^{14}C-glycocholate breath tests have been positive in some patients, which might indicate the presence in the small bowel of bacteria that deconjugate bile salts.[4 7] These reports have stressed, however, that bacterial overgrowth seems to be an occasional feature rather than an overall mechanism for diarrhoea. Other bacteriological studies on patients with diabetic diarrhoea have elicited little evidence for a contaminated small-bowel syndrome.[3 8 9] Bile-salt malabsorption has also been suggested, in a report of clinical improvement with cholestyramine.[10] There have apparently been no other controlled clinical trials of patients taking cholestyramine, and bile-salt metabolism has not been studied in these patients.

We have examined the duodenal bile-salt concentration, size of the bile-salt pool, and faecal excretion of bile in diabetics.

Patients and methods

We studied three groups of patients, from whom informed consent was obtained. Group 1 comprised 18 stable, uncomplicated diabetics treated with insulin or diet, who served as controls; group 2 comprised 12 diabetics treated with insulin who had evidence of peripheral or autonomic neuropathy but no history of diarrhoea; and group 3 comprised seven diabetics receiving insulin who had diabetic diarrhoea at the time of study and evidence of peripheral and autonomic neuropathy.

The size of the bile-salt pool was estimated by a method similar to that of Duane *et al.*[11] The patients were given 5 μCi of 24-[^{14}C]-cholic acid and 5 μCi of 24-[^{14}C]-chenodeoxycholic acid intravenously the night before the study. In the morning a tube was positioned fluoroscopically below the ligament of Treitz and an unstimulated fasting sample of duodenal bile taken. A further sample was taken after a test meal containing 50 g of fat. When necessary suitable corrections were made against the percentage of the ^{14}C dose excreted in 72 hours. Bile salts were separated by thin-layer chromatography and assayed using the method of Bruusgaard.[12] Bile salts were extracted from three-day stool collections,[13] and the percentage of ^{14}C dose excreted in 72 hours was measured by liquid scintillation spectrometry with automatic external standardisation to correct for quenching. Faecal 3α-hydroxy bile acids were measured using 3α-hydroxysteroid dehydrogenase. The presence of free bile acids in duodenal aspirates was detected by means of thin-layer chromatography,[12] and bile-acid spots were developed in 10% phosphomolybdic acid in ethanol. The rate of failure of intubation was high, especially in patients with autonomic neuropathy. Radioactive bile salts were not given in the initial part of the study. The significance of results (given as means ±SE of mean) was evaluated with the Wilcoxon rank-sum test.

Results

All three groups were closely matched for age. The duration of diabetes was greatest in group 3. Faecal fat was also increased in this group, though not significantly (table I).

The ratio of trihydroxy to dihydroxy bile salts was significantly altered in groups 2 ($P < 0.05$) and 3 ($P < 0.01$) compared with group 1. The mean glycine to taurine ratio was highest in group 3, although this value (4·1 ± 0·9) was within the normal range.[14] The size of the bile-salt pool was significantly higher in group 2 ($P < 0.05$). The mean pool size in group 3 (4·772 ± 0·584 mmol) was lower than that in group

TABLE I—*Clinical details of the three groups of diabetics (results expressed as means ± SE of mean)*

Group	Sex	Age in years	Duration of diabetes (years)	Faecal fat (mmol/24 h)
1—Diabetics treated with insulin or diet, with no complications (controls)	9M, 9F	53·4 ± 4·0 (n = 17)	6·9 ± 1·8 (n = 18)	11·6 ± 2·9 (n = 13)
2—Diabetics with neuropathy and no diarrhoea	7M, 5F	56·2 ± 3·7 (n = 12)	12·9 ± 1·8 (n = 12)	13·9 ± 3·9 (n = 10)
3—Diabetics with diarrhoea	6M, 1F	56·4 ± 4·2 (n = 7)	19·5 ± 2·6 (n = 7)	25·7 ± 6·8 (n = 6)

Conversion: SI to traditional units—Faecal fat: 1 mmol/24 h ≈ 0·284 g/24 h.

TABLE II—*Analysis of size and composition of bile-salt pool in each group (results expressed as mean ± SE of mean)*

	Control group	Diabetics with neuropathy	Diabetic diarrhoea
Total duodenal bile acids (mmol/l)	6·6 ± 1·1 (n = 15)	8·1 ± 2·5 (n = 8)	8·2 ± 1·3 (n = 6)
Glycine : taurine ratio	2·5 ± 0·4 (n = 15)	3·3 ± 1·2 (n = 8)	4·1 ± 0·9 (n = 6)
Trihydroxy : dihydroxy bile acid ratio	1·25 ± 0·1 (n = 15)	0·80 ± 0·09* (n = 8)	0·55 ± 0·09** (n = 6)
Pool size (mmol)	6·672 ± 0·389 (n = 5)	10·510 ± 0·763* (n = 3)	4·772 ± 0·584 (n = 3)
% of ^{14}C dose excreted in 72 hours	6·9 ± 2·3 (n = 7)	11·2 ± 5·7 (n = 5)	49·9 ± 13·4** (n = 3)
Faecal bile acids (mmol/24 h)	0·900 ± 0·181 (n = 5)	2·475 ± 0·160* (n = 5)	2·810 ± 0·289* (n = 5)

*$P < 0.05$. **$P < 0.01$.

Conversion: SI to traditional units: Duodenal bile acids: 1 mmol/l ≈ 37-53 mg/100 ml. Faecal bile acids: 1 mmol/24 h ≈ 0·37-0·53 g/24 h.

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1 (6·672 ± 0·389 mmol), but the difference was not significant ($P < 0·1$). The percentage ^{14}C dose excreted in 72 hours was significantly increased in group 3 ($P < 0·01$), and the faecal total 3α-hydroxy bile salts were increased in both group 2 ($P < 0·05$) and group 3 ($P < 0·05$) (table II).

We found evidence of bile-salt deconjugation in one of six patients from group 2 and one of six from group 3. None of 15 patients in group I had free bile acids in their duodenal aspirate.

Discussion

Studies that necessitate intubating diabetics with autonomic neuropathy are seldom carried out because of the technical difficulties and the relative rarity of the disease. Although many aspects of gastrointestinal function have been examined in detail,[2 3 8 9 15] bile-salt metabolism in this syndrome has not been reported. A recent report on cholesterol metabolism in diabetes[16] showed that the bile-salt pool was larger and faecal bile-acid excretion higher during uncontrolled hyperglycaemia than during euglycemia due to insulin treatment. These findings were attributed to an overall increase in lipid production. Our results in patients with autonomic neuropathy but no diarrhoea were similar, since we also found an increased pool size and a higher faecal excretion of bile. All our patients, however, had reasonably well-controlled diabetes during the study. Large pool sizes also occur in coeliac disease[17] and obesity.[18] Abnormalities leading to impaired gall-bladder function[17] appear to provide the mechanism for this effect in coeliac disease. Diabetics have a high incidence of gall-bladder atony,[19 20] and so a mechanism similar to that of coeliac disease is possible. Mok[18] suggested that a sluggish recycling frequency in obese patients tends to increase the bile-salt pool. In general, diabetics with autonomic neuropathy are believed to have decreased intestinal motility,[3 21] which might tend to reduce the recycling frequency and thus increase the pool size.

Comparison of the results in the patients with diabetic diarrhoea with those in the control group suggest a mechanism of bile-salt malabsorption, since altered glycine to taurine and trihydroxy to dihydroxy ratios, a smaller pool, and increased faecal excretion have all been found to varying degrees in malabsorption syndromes.[22 23] We did not attempt to separate the dihydroxy components in our specimens, so the question remains whether there is a rise in deoxycholate concentrations due to increased contact with colonic bacteria or whether the rate of hepatic synthesis of bile salts is altered in these patients. We found little evidence of the contaminated small-bowel syndrome as judged by the presence in duodenal aspirate of free bile acids, although altered bile-salt composition is a feature of this syndrome.[24] Patients with postvagotomy diarrhoea often have symptoms similar to those of diabetic diarrhoea, and show bile-salt malabsorption[25] and respond to cholestyramine.[10 26] Our results support the hypothesis[10] that diabetic diarrhoea is similar to postvagotomy diarrhoea. At present, although the mechanisms are not clear, it appears that in diabetic diarrhoea changes occur in the bile-salt profile in that the loss of faecal bile becomes considerably greater than normal and the pool size is reduced.

This study did not include any patients temporarily free of diarrhoea, so it would be interesting to see whether the pool size returns to normal or stabilises at an abnormally high level. If the latter occurs, one could postulate a link between cycles of abnormally high pools of bile salts and bouts of watery diarrhoea. Our results indicate that the idiopathic diarrhoea of diabetes may sometimes be choleretic, in which case cholestyramine may be a rational treatment.

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ONE HUNDRED YEARS AGO In the *Virginia Medical Journal* for May, Mr J B Hodgkin maintains that the loss of teeth by caries is peculiar to the human race, and to the most civilised portions of that race; and that it befalls the Anglo-Americans to a much greater extent than any other branch of the human family. Dyspepsia, an acid condition of the secretions of the mouth, and the decomposition of particles of food retained in the mouth, will not, he thinks, explain this state of matters, for the teeth of domesticated animals, which are exposed to similar dietetic conditions, are not attacked by decay. He is inclined to attribute the frailty of Anglo-American teeth to unhealthy conditions of Anglo-American parents, and particularly of Anglo-American mothers, who live lives of languor and debility when the foundations of the teeth are being laid down. Whatever mischief is done in this way to other tissues may be to a great extent rectified after birth by good nursing and sound hygiene; but the teeth, when once formed, can undergo no change of a physiological character, but must remain as when first calcified. The teeth which are first formed are the first to be destroyed by caries. The temporary teeth are often attacked in the first year of their eruption. The first permanent molars are almost as readily destroyed; but the canines and wisdom teeth, which are matured in extra-uterine life, are the most enduring of all. Mr Hodgkin arrives at the conclusion that the great predisposing cause of the decay of the teeth of Anglo-Americans is defective intra-uterine nutrition. (*British Medical Journal*, 1878.)