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Complex carbohydrate malabsorption in exocrine pancreatic insufficiency

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Abstract

The magnitude of complex carbohydrate malabsorption in exocrine pancreatic insufficiency has not been well quantified in the past. The quantity of carbohydrate malabsorbed after a rice starch (100 g) meal in 20 patients with chronic pancreatitis (n=10) or pancreatic cancer (n=10) was therefore estimated. Patients had a three day stool fat collection (80 g/24 hour fat intake), a lactulose (20 g), and a rice flour (100 g) breath hydrogen test. Normal controls (n=29) had a postprandial H_2 increase ≤14 ppm and malabsorbed (mean (SEM)) 1·12 (0·44) (range 0–11·10) g of the 100 g of carbohydrate ingested. Patients malabsorbed significantly more carbohydrate (11·36 (2·23) (range 8·90–32·60) g, $F_{1,47}$= 29·92, p<0·001). The number of patients with fat (>7 g, n=8) or carbohydrate (increase in H_2≥20 ppm, n=10) malabsorption was not different (χ^2=0·10, p=0·75). There was a significant correlation between faecal fat and amount of malabsorbed carbohydrate (r=0·60, $F_{1,17}$=9·70, p=0·006) and faecal fat and stool wet weight (r=0·57, $F_{1,18}$=8·67, p<0·009), but not between stool wet weight and amount of malabsorbed carbohydrate (r=0·28, $F_{1,17}$=1·45, p=0·25). Although patients with exocrine pancreatic insufficiency malabsorb 10%–30% of the ingested complex carbohydrate, the main determinant of stool wet weight could be faecal fat.

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Although malabsorption of fat and protein have been extensively investigated, malabsorption of complex carbohydrate has not attracted much attention in patients with exocrine pancreatic insufficiency. Based on pioneer work by Fogel and Gray,[1] the notion that symptomatic carbohydrate malabsorption is uncommon in patients with chronic pancreatitis[2 3] has not been challenged until recently, when it has been noticed that patients with exocrine pancreatic insufficiency may malabsorb complex carbohydrate.[4–7]

As the magnitude of this carbohydrate malabsorption has not been investigated, the aim of the present study was to quantify the extent of complex carbohydrate malabsorption in patients with chronic pancreatitis and cancer of the pancreas.

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Methods

SUBJECTS

Twenty ambulatory patients (16 men, four women) with a mean (SEM) age of 50·70 (2·36) (range 39–72) years, suffering from chronic idiopathic pancreatitis (n=10) or pancreatic cancer (n=10) and suspected malabsorption syndrome, participated in the study (Table I).

None of the patients were alcoholic or had any history of small intestinal disease, gastric operation, or small bowel resection and had not lost more than 10% of body weight in the six months preceding the study. Diagnosis of pancreatic disease was made by both computed tomography (CT) and endoscopic retrograde cholangiopancreatography (ERCP) in all patients and documented at laparotomy in those with pancreatic cancer. Twenty nine normal volunteers (18 men, 11 women) with a mean (SEM) age of 36·66 (2·28) (range 20–60) years served as controls. None of the patients or the normal volunteers had received antibiotics in the two weeks before the test period.

All 49 subjects participated in this study after giving written informed consent. The protocol was approved by the ethics committee on human studies of the Department of Internal Medicine, University of Athens, in December 1985.

TESTS PERFORMED

Quantitative faecal fat excretion

All 20 patients were placed on a 2200 kcal diet containing 80 g/day of fat. This diet was consumed for six days. Stools were quantitatively collected for the last three days (72 hours) of the test. After stool wet weight had been measured, they were analysed for fat content by the Van de Kramer method.[8] Stool wet weight and fat content were expressed as g/24 hours. The excretion of normal subjects is less than 7 g/24 hours.

TABLE I *Patients with suspected pancreatic malabsorption*

No	*Sex*	*Age (y)*	*Diagnoses*	*Stool weight (g/24 h)*	*Stool fat (g/24 h)*
1	F	41	Pancreatic cancer	142	13·7
2	M	72	Pancreatic cancer	333	25·0
3	M	40	Chronic pancreatitis	157	13·8
4	M	61	Pancreatic cancer	387	8·6
5	F	69	Pancreatic cancer	282	18·2
6	M	45	Chronic pancreatitis	351	19·1
7	M	48	Pancreatic cancer	195	16·5
8	M	55	Pancreatic cancer	280	9·5
9	M	54	Pancreatic cancer	111	0·3
10	M	65	Pancreatic cancer	185	1·4
11	M	41	Chronic pancreatitis	267	5·6
12	M	41	Pancreatic cancer	160	5·3
13	M	40	Chronic pancreatitis	233	7·0
14	M	45	Chronic pancreatitis	93	3·3
15	M	59	Chronic pancreatitis	127	6·0
16	M	44	Chronic pancreatitis	195	6·5
17	F	58	Pancreatic cancer	162	4·2
18	M	39	Chronic pancreatitis	202	7·0
19	F	42	Chronic pancreatitis	154	4·2
20	M	55	Chronic pancreatitis	210	6·1

Complex carbohydrate malabsorption

After an overnight (12–14 hours) fast all subjects drank a solution of 20 g lactulose in 250 ml of water. Three days later the same subjects again fasted and then ate a standard meal of rice cake made of 100 g rice flour, one egg, butter (7 g), and baking powder (5 g). This meal has been shown to be totally absorbed producing less than 20 parts per million (ppm) of peak breath H_2 concentration, when consumed by normal volunteers.[5 9 10]

After the ingestion of the lactulose drink or the rice flour meal end expiratory breath samples were collected in 50 ml polyethylene syringes at time 0 and 15 minute intervals thereafter over a 5·5 or seven hour period for the lactulose or the rice flour test respectively. During the test periods subjects were instructed not to smoke[11] or eat anything[12] but drank water ad libitum. Breath H_2 concentration was measured with a research chromatography (Hewlett-Packard 5750G) equipped with a thermal conductivity detector. The operating conditions have been published elsewhere.[13] The minimum H_2 concentration detectable was 3 ppm, which gave a recorder deflection of 2 mm.

DEFINITIONS, CALCULATIONS, AND STATISTICS

Carbohydrate malabsorption was defined as an increase of breath H_2 concentration $\geq$20 ppm over the base line. The amount of carbohydrate malabsorbed was estimated by comparing the area under the breath hydrogen curve (BH_2AUC) after the rice flour meal with that after lactulose.[9 14] Lactulose, a non-absorbable disaccharide, is rapidly metabolised on entering the colon by the colonic flora into H_2, CH_4, CO_2, and short chain fatty acids. The H_2 produced in the colon is absorbed and excreted in the breath. It has been shown that there is a rough linear correlation between breath H_2 excretion rate and the quantity of malabsorbed carbohydrate.[9 14] As it has been assumed that equal amounts of lactulose or other carbohydrate malabsorption will produce equal changes in breath H_2 excretion,[9] rice starch malabsorption has been calculated as g malabsorbed carbohydrate according to the formula:

$$\frac{BH_2AUC-\text{rice}}{BH_2AUC-\text{lactulose}}\times 20\,g$$

The BH_2AUC was calculated by the trapezoid rule.[15 16]

Results in the text and figures are presented as mean (SEM). The statistical significance of the results was assessed by one way analysis of variance (ANOVA), χ^2 test and regression analysis as appropriate.[17] Probabilities of $<0{\cdot}05$ were regarded as significant.

TABLE II *Breath H_2 data of the 20 patients with suspected pancreatic malabsorption*

No	*Lactulose breath H_2 test*			*Rice flour breath H_2 test*			*Rice starch malabsorption (g or %)*
	Fasting (ppm)	*ΔH_2 (ppm)*	*Area (ppm/4 h)*	*Fasting (ppm)*	*ΔH_2 (ppm)*	*Area (ppm/4 h)*	
1	10	188	416	3	78	186	8·9
2	63	77	212	0	95	213	20·1
3	16	46	73	39	47	119	32·7
4	0	78	218	5	72	150	13·7
5	12	77	179	12	56	129	14·4
6	4	64	179	10	77	174	19·5
7	12	42	78	22	54	127	32·6
8	2	88	197	15	89	141	14·4
9	0	89	213	6	30	63	12·5
10	1	77	208	4	34	148	14·2
11	0	1	NHP	9	9	–	–
12	0	27	87	4	9	9	2·1
13	8	30	66	9	5	20	6·0
14	15	47	107	15	9	28	5·3
15	19	77	139	26	11	36	5·1
16	12	36	99	12	9	11	2·2
17	8	37	82	1	0	0	0
18	1	44	113	8	0	0	0
19	2	45	86	10	13	40	9·2
20	9	88	138	25	13	21	3·0

NHP=non-hydrogen producer.

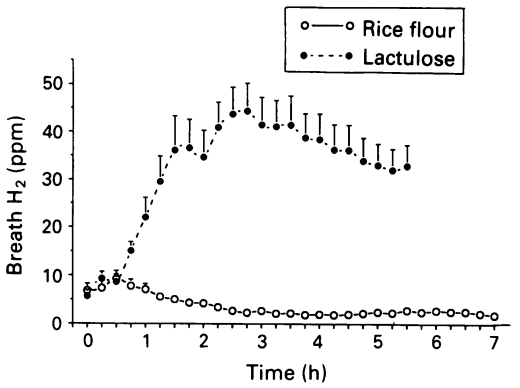

Figure 1: Mean (SEM) breath H_2 curves of 29 normal volunteers after ingestion of lactulose (20 g) or rice flour (100 g).

Results

All subjects consumed the lactulose drink within five minutes and the rice flour pancake within 15 minutes. Most of them complained about the taste of lactulose and the amount of the pancake but consumed it all.

Figure 1 shows the mean (SEM) breath H_2 curve, after lactulose or the rice flour meal, of normal volunteers. The mean postprandial increase in breath H_2 after the rice flour meal was 2·93 (0·72) (range 0–14) ppm. When comparing the area under the breath H_2 curve after the rice flour meal with that of lactulose, normal subjects malabsorbed 1·12 (0·44) (range 0–11·10) g of carbohydrate.

Tables I and II show diagnoses, stool fat, and wet weight, as well as breath H_2 excretion data of the 20 patients and Figure 2 shows the mean (SEM) breath H_2 curves after lactulose or rice

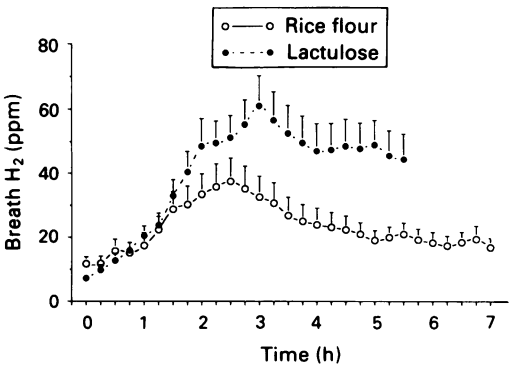

Figure 2: Mean (SEM) breath H_2 curves of 20 patients with chronic pancreatitis or pancreatic cancer after ingestion of lactulose (20 g) or rice flour (100 g).

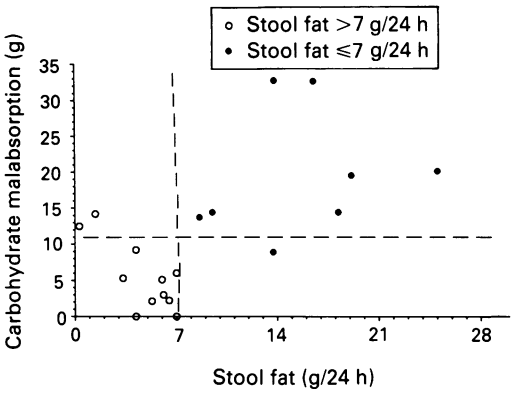

Figure 3: Correlation of stool fat (g/24 h) with the amount of carbohydrate malabsorbed (g) ($y=3{\cdot}25+0{\cdot}88x$, $r=0{\cdot}60$, $F_{1,17}=9{\cdot}70$, $p=0{\cdot}006$) in 20 patients with chronic pancreatitis or pancreatic cancer. Dotted lines represent the upper range of normal values.

flour ingestion. One patient was an occasional non-H_2 producer, as he did not produce breath H_2 after lactulose, but he had an increase in H_2 of 9 ppm after the rice flour meal. His faeces produced significant amounts of H_2 when they were incubated in vitro with lactulose. Patients malabsorbed significantly more carbohydrates (11·36 (2·23) range 8·90–32·60) g) compared with normal volunteers ($F_{1,47}=29{\cdot}92$, $p<0{\cdot}001$). The number of patients with carbohydrate (increase in $H_2 \geq 20$ ppm, n=10) or fat (>7 g/24 hours, n=8) malabsorption was not significantly different ($\chi^2=0{\cdot}10$, $p=0{\cdot}75$). Patients with an increase in $H_2 \geq 20$ ppm malabsorbed 18·30 (2·60) g of carbohydrate and those with >7 g/24 hours of faecal fat malabsorbed 15·55 (1·90) g of fat.

There was a significant correlation between faecal fat and amount of malabsorbed carbohydrate ($y=3{\cdot}25+0{\cdot}88x$, $r=0{\cdot}60$, $F_{1,17}=9{\cdot}70$, $p=0{\cdot}006$) (Fig 3), as well as between faecal fat and stool wet weight ($y=146{\cdot}70+7{\cdot}13x$, $r=0{\cdot}57$, $F_{1,18}=8{\cdot}67$, $p<0{\cdot}002$), but not between stool wet weight and amount of malabsorbed carbohydrate ($r=0{\cdot}28$, $F_{1,17}=1{\cdot}45$, $p=0{\cdot}25$).

Discussion

Recently it has been shown that normal volunteers efficiently absorb an oral load of 100 g of rice starch with minimal generation of breath H_2.[5 9 18] These results proved to be reproducible in the present study, indicating that a cut off value of ≥ 20 ppm of H_2 increase is a safe indicator of rice starch malabsorption. Kerlin *et al*[5] were the first to use the rice flour breath H_2 test to study complex carbohydrate malabsorption in diseases of the pancreas and small intestine. They have shown that patients with chronic pancreatitis or pancreatic cancer may malabsorb carbohydrate,[5] but the amount malabsorbed had not been quantified. Even more recently Hammer *et al*[6] measured the magnitude of faecal carbohydrate excretion in five patients with exocrine pancreatic insufficiency. They showed that three of the five patients had excessive faecal excretion of carbohydrate and organic acids.

Although the breath H_2 test is sensitive and non-invasive and widely applied for the study of carbohydrate malabsorption, there are certain problems in the interpretation of its results. It is assumed that the H_2 producing bacteria are limited to the colon and that the fermentation of carbohydrates occurs rapidly on entering the caecum. There is a wide interindividual variation, however, in breath H_2 excretion, when given a constant dose of lactulose repeatedly. It is also assumed that all complex carbohydrate malabsorbed are converted to H_2 with the same degree of rapidity as is the case with lactulose. There are indications that certain complex carbohydrates such as fibre are converted to H_2 more slowly and less completely than lactulose[9] resulting in an underestimation of the amount entering the colon. Another problem that researchers face when using breath H_2 tests is their duration. Many volunteers complain when fasted for more than six hours. As a result, most experiments end after six to eight hours, when the breath H_2 concentration has not returned to the fasting value. All these assumptions and practical problems concerning the breath H_2 test have been discussed in detail by Bond and Levitt[14] and Levitt *et al*[9] who suggest that 'quantitative data of the breath H_2 test should be considered to be estimates of malabsorption of fermented material rather than precise quantitative measurements of polysaccharide malabsorption'. Despite its limitations, the breath H_2 test is the only acceptable non-invasive method to estimate complex carbohydrate malabsorption in humans.[9 14 19]

In the present study, it has been shown that 50% of the patients with chronic pancreatitis or pancreatic cancer had evidence of polysaccharide malabsorption (increase in $H_2 \geq 20$ ppm) and malabsorbed 10%–30% of the ingested complex carbohydrate. This finding challenges the notion that carbohydrate malabsorption is uncommon in patients with chronic pancreatitis.[1-3] Recent experimental data support our results suggesting that faecal pancreatic type isoamylase activity is lower in patients with chronic pancreatitis and pancreatic cancer who have moderate to severe exocrine pancreatic insufficiency when compared with normal subjects.[20] In these patients gastric acidity does not affect faecal pancreatic isoamylase activity, but faecal salivary type isoamylase activity is raised in patients with gastric hypoacidity, indicating the important role of H_2 receptor antagonist administration with pancreatic supplements.

All our patients who had evidence of fat malabsorption (faecal fat >7 g/24 hours) malabsorbed complex carbohydrate (increase in H_2 ≥ 20 ppm) as well, and there was a significant correlation between faecal fat and amount of malabsorbed carbohydrate. This correlation is explained if there is a parallel reduction of pancreatic lipase and colipase combined with low pancreatic type isoamylase secretion. Indeed, Moriyoshi *et al* have shown that there is a good positive correlation between faecal pancreatic isoamylase activity and grade of pancreatic exocrine insufficiency as assessed by the secretin test.[20]

The second important finding from this study is the significant correlation between faecal wet weight and stool fat. Similarly a significant correlation between these two variables can be calculated from the data shown in Table I in the study by Kerlin *et al*[5] ($y=117{\cdot}99+5{\cdot}58x$, $r=0{\cdot}81$, $F_{1,15}=27{\cdot}72$, $p<0{\cdot}001$) who investigated rice flour absorption in patients with chronic pancreatitis, and from the data shown in

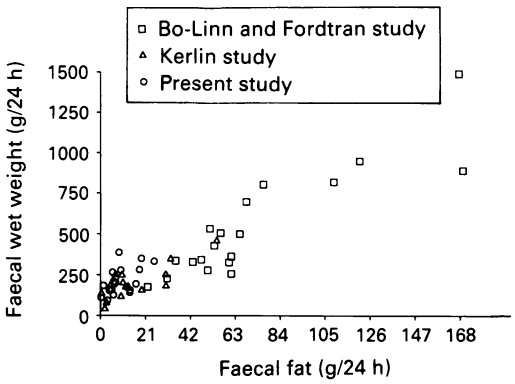

Figure 4: Correlation of faecal fat with faecal wet weight in 56 patients suffering from chronic pancreatitis or pancreatic cancer ($y=122{\cdot}89+6{\cdot}18x$, $r=0{\cdot}91$, $F_{1,54}=275{\cdot}70$, $p<0{\cdot}001$). With kind permission of the authors[5 21] and the publisher of Gastroenterology, WB Saunders Co to include their data in this figure.

Table I (patients 1 to 19) in the study by Bo-Linn and Fordtran[21] ($y=38{\cdot}54+7{\cdot}07x$, $r=0{\cdot}89$, $F_{1,17}=67{\cdot}57$, $p<0{\cdot}001$) who investigated faecal fat concentration in patients with pancreatic steatorrhoea. Figure 4 shows the correlation between faecal wet weight and stool fat of the pooled data derived from these two studies as well as the present study. This significant correlation between faecal fat and wet weight indicates that malabsorption of fat could be the main determinant of faecal weight in patients with mild to moderate exocrine pancreatic insufficiency. Despite this evidence, patients with severe exocrine pancreatic insufficiency (faecal fat 40–120 g/day) may have osmotic diarrhoea due to carbohydrate malabsorption.[6] In patients with mild to moderate pancreatic insufficiency, however, there is no correlation between the amount of complex carbohydrate malabsorbed and stool wet weight. This is explained if malabsorbed polysaccharides are fermented to short chain fatty acids, most of which are rapidly absorbed,[22] decreasing the colonic osmotic pressure and thereby preventing an increase in faecal water.

In conclusion, we have shown that patients with chronic pancreatitis or pancreatic cancer, who have mild to moderate fat malabsorption, may malabsorb up to one third of the ingested carbohydrate. These malabsorbed carbohydrates are probably metabolised by the colonic flora to short chain fatty acids and subsequently absorbed by the colon, so that malabsorbed fat could be the main determinant of faecal weight.

We thank the publisher of Gastroenterology, W B Saunders Co, Professor Paul Kerlin, and Professor John S Fordtran for granting permission to include data of their publications[5 21] in Figure 4 of this paper, as well as Dr Peter E T Isaacs, MD, MRCP, for his criticism and helpful suggestions during the preparation of the manuscript.

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