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Lower gastrointestinal symptoms are associated with worse glycemic control and quality of life in type 1 diabetes mellitus

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ABSTRACT

Objectives Lower gastrointestinal symptoms are not well characterized in people with type 1 diabetes, and the effects on quality of life and glycemic control are unknown. This study aimed to determine the prevalence of lower gastrointestinal symptoms and the effects on glycemic control and quality of life, and to investigate for underlying causes.

Research design and methods This is a prospective, cohort study in secondary care. Patients with type 1 diabetes completed a gastrointestinal symptom questionnaire and the Short Form 36 V.2 quality of life questionnaire and had their hemoglobin A1c measured. Patients with diarrhea were offered reassessment and investigation as per the national guidelines. Controls without diabetes were used to compare symptom prevalence and quality of life scores.

Results 706 with type 1 diabetes (mean age 41.9 years) and 604 controls (mean age 41.9 years) were enrolled. Gastrointestinal symptoms were significantly more frequent in type 1 diabetes compared with controls, in particular constipation (OR 2.4), diarrhea (OR 2.5), alternating bowel habit (OR 2.1), abdominal pain (OR 1.4), floating stools (OR 2.7), bloating (OR 1.4) and flatulence (OR 1.3) (all $p<0.05$). Previous pancreatitis was more frequent in type 1 diabetes (OR 4.6), but other gastrointestinal conditions were not. Gastrointestinal symptoms were associated with poorer glycemic control ($p<0.01$) and worse quality of life particularly in those with diarrhea. Investigation of those with diarrhea, including those with alternating bowel habit, (n=105), identified a cause in 72.3% with subsequent change in management.

Conclusions Gastrointestinal symptoms are twice as common in type 1 diabetes and associated with poorer quality of life and glycemic control. Investigation of diarrhea in people with type 1 diabetes leads to a high yield of treatable conditions and a change in management in about three-quarters.

Significance of this study

What is already known about this subject?

- Gastrointestinal symptoms occur in people with diabetes, but the true prevalence is unknown and the underlying causes of diarrhea in diabetes are not well characterized.

What are the new findings?

- Lower gastrointestinal symptoms are twice as common in people with diabetes and are associated with worse glycemic control and quality of life.
- Focused investigations lead to treatable causes in over two-thirds of those with diarrhea.

How might these results change the focus of research or clinical practice?

- A low threshold for investigating gastrointestinal symptoms in people with type 1 diabetes may lead to improvement in glycemic control and quality of life.

INTRODUCTION

Long-term complications cause major morbidity and mortality in type 1 diabetes mellitus.[1] Intensive glycemic control can reduce long-term complications and improve quality of life.[1 2] Even with good glycemic control, complications occur, suggesting other factors increase the risk.[3] Coexisting medical problems are a significant confounding factor when managing patients' glycemic control.[3] The association between type 1 diabetes and the gastrointestinal tract was first described in 1936 by Bargen.[4] Classically, this has been described as *diabetic diarrhea* and most commonly occurs in patients with type 1 diabetes mellitus.[4] Despite this historical description there have been very few studies examining patients with type 1 diabetes specifically for lower gastrointestinal symptoms.

A postal survey of 15 000 people from Australia suggested that patients with diabetes are more likely to have gastrointestinal symptoms than the general population. Critically, although the survey comprises an initial attempt to question 15 000 individuals, there was a 60% response (n=8657) and only 27 of the respondents had type 1 diabetes. Furthermore, glycemic control and gastrointestinal

symptoms were self-reported and no investigations were performed.[5] Despite these limitations this study reported that both upper and lower gastrointestinal symptoms were significantly more common in patients with diabetes compared with controls.[5] A further study found that gastrointestinal symptoms in patients with diabetes were associated with poor glycemic control (glycosylated hemoglobin was measured in a subgroup) and peripheral neuropathy.[6] This group has subsequently suggested no association between glycemic control and gastrointestinal symptoms.[7] This study only included 136 individuals of whom a minority (n=7) had type 1 diabetes and glycemic control was self-reported. The concept of gastrointestinal symptom cycling in patients with diabetes has been proposed and is associated with psychological factors rather than glycemic control.[8]

There is a paucity of data regarding gastrointestinal symptoms in patients with type 1 diabetes, in particular regarding prevalence, underlying causes and pathophysiology.

Several mechanisms have been implicated in the pathogenesis of gastrointestinal symptoms, including *Helicobacter pylori* infection,[9] psychological factors,[10] and impaired sensory function.[11 12] However, disordered motor function resulting from autonomic neuropathy[13 14] and abnormal blood glucose levels also seem to be important. Acute changes in blood glucose concentrations can have an effect on motor function throughout the gastrointestinal tract[15 16] and modulate sensory perception.[17–20] An association between gastrointestinal symptoms and glycemic control is also supported by cross-sectional epidemiologic studies.[6 21]

The mechanism by which diabetes may lead to diarrhea is thought to be multifactorial, and most hypotheses include autonomic dysfunction and alteration of regulatory enterohumoral responses.[22] Type 1 diabetes is also associated with a number of conditions which could lead to diarrhea, including celiac disease,[23] exocrine pancreatic insufficiency,[24] thyroid dysfunction,[25] IgA deficiency[26] and small bowel bacterial overgrowth.[27] Although these associations have been independently reported, there has never been a unifying assessment of a large cohort of patients with type 1 diabetes and diabetic diarrhea.

This area deserves investigation as gastrointestinal symptoms are likely to impact on quality of life and glycemic control. The aims of this study were to determine the prevalence of gastrointestinal symptoms in patients with type 1 diabetes and to determine the correlation between such symptoms, glycemic control and quality of life. Furthermore, a subgroup with significant diarrhea was investigated to determine underlying causes.

RESEARCH DESIGN AND METHODS

The Sheffield Diabetes Centre operates at the Royal Hallamshire Hospital and the Northern General Hospital, Sheffield, UK, comprising approximately 2000 patients registered with a diagnosis of type 1 diabetes. Type 1 diabetes was defined as per the American Diabetes Association position statement.[28] Therefore patients were considered to have type 1 diabetes if they presented at an early age, with diabetic ketoacidosis or progressed onto insulin within 12 months. If autoantibody profiles were available, then these were also considered. Where diabetes type was uncertain, the notes were reviewed with the treating physician and a decision made concerning diabetes type. If diabetes type was still uncertain, then the individual was not invited to participate.

Inclusion criteria

The study includes patients with type 1 diabetes over the age of 16 years.

Exclusion criteria

The exclusion criteria include age of less than 16 years and inability to give consent.

Initial assessment

Participants completed a previously validated gastrointestinal symptom questionnaire which has been used in local studies[29] to assess the presence and degree of symptoms, as well as document other relevant diagnoses. Diarrhea was defined as greater than three stools per day and constipation as less than three stools per week as per the British Society of Gastroenterology guidelines.[30] Quality of life was assessed using the Short Form 36 V.2 questionnaire and blood was taken for hemoglobin A1c (HbA1c).

Control group

During the same time period a control group was recruited from the general population and the same questionnaires were completed. These individuals were recruited from local shopping centers and supermarkets during daylight hours. This group was selected to compare with type 1 diabetes as the majority seen as outpatients for diabetes review are able-bodied.

Investigations for subgroup with diarrhea

Individuals with type 1 diabetes and diarrhea (including those with alternating bowel habits) were recalled and offered investigation. All individuals underwent a standard protocol of investigations, including celiac serology (and duodenal biopsy in positive cases), fecal elastase-1 measurement, glucose hydrogen breath testing and ileocolonoscopy. Individuals with positive findings on investigation were reviewed and relevant treatment was started.

Statistical analysis

The frequency of gastrointestinal symptoms in individuals with type 1 diabetes was compared with the controls and was expressed as ORs with 95% CIs. Frequencies were compared using χ^2 testing or Fisher's exact if n<10 in any category. Glycemic control was assessed using median HbA1c in those with type 1 diabetes with symptoms compared with age-matched and sex-matched controls with type 1 diabetes but no symptoms. The median quality of life scores in those with type 1 diabetes and

Table 1 Clinical characteristics of participants with type 1 diabetes mellitus

Variable	Type 1 diabetes
Mean age	41.9 years (95% CI 39.8 to 44.0)
Number of men	390/706 (55.2%)
Mean hemoglobin A1c	8.27 (SD 1.68)
Self-reported complications (%)	
Retinopathy	249 (35.3)
Nephropathy	55 (7.8)
Peripheral neuropathy	133 (18.8)

symptoms were compared with the age-matched and sex-matched individuals with type 1 diabetes and no symptoms. Additionally, controls without diabetes with the same symptoms and controls with no symptoms were age-matched and sex-matched to these individuals with type 1 diabetes. The Kruskal-Wallis test, and if significant the Mann-Whitney U test, was applied.

RESULTS

Seven hundred and six participants with type 1 diabetes (mean age 41.9 years, 95% CI 39.8 to 44.0, 390 men) and 604 controls without diabetes (mean age 41.9 years, 95% CI 40.5 to 43.4, 279 men) were included (characteristics are shown in table 1).

Overall 440/706 (62.3%, 95% CI 58.6 to 65.9) individuals with type 1 diabetes reported gastrointestinal symptoms compared with 284/604 (47.0%, 95% CI 42.9 to 51.1) controls, giving an OR of 1.9 (1.5–2.3, p<0.0001). The results of a further analysis of individual symptom frequencies and known medical conditions in people with type 1 diabetes compared with controls are shown in table 2.

Table 2 Prevalence of gastrointestinal symptoms and known medical conditions in people with type 1 diabetes and comparison with controls

Symptom	Type 1 diabetes	Controls	OR (95% CI)	P values
Normal bowel habit	541 (76.6%)	540 (89.4)	0.4 (0.3 to 0.6)	<0.001
Constipation	60 (8.5%)	20 (3.3%)	2.4 (1.4 to 4.1)	<0.001
Diarrhea	43 (6.1%)	16 (2.6%)	2.5 (1.4 to 4.5)	0.0017
Alternating bowel habit	62 (8.8%)	27 (4.5%)	2.1 (1.3 to 3.4)	0.0013
Flatulence	231 (34.9%)	174 (28.8%)	1.3 (1.0 to 1.7)	0.02
Bloating	203 (30.7%)	146 (24.2%)	1.4 (1.1 to 1.8)	0.009
Floating stools	84 (12.7%)	31 (5.1%)	2.7 (1.8 to 4.1)	<0.001
Weight loss	76 (11.5%)	34 (5.6%)	2.2 (1.4 to 3.3)	0.0002
Abdominal pain	117 (17.7%)	81 (13.4%)	1.4 (1.0 to 1.9)	0.037
TATT	247 (37.3%)	100 (16.6%)	3.0 (2.3 to 3.9)	<0.001
Celiac disease	2	4	0.4 (0.1 to 2.3)	NS
Anemia	92	53	1.5 (1.1 to 2.2)	0.012
Thyroid	87	20	4.1 (2.5 to 6.8)	<0.0001
Primary biliary cirrhosis	1	0	NA	NS
Sjogren's	2	0	NA	NS
Dermatitis herpetiformis	3	0	NA	NS
Osteoporosis	15	12	1.1 (0.5 to 2.3)	NS
Epilepsy	15	3	4.3 (1.3 to 15.1)	0.015
Neurologic disease	29	11	2.3 (1.1 to 4.7)	0.023
Previous pancreatitis	16	3	4.6 (1.3 to 16.0)	0.0009
Irritable bowel syndrome	74	48	1.4 (0.9 to 2.0)	NS
Diverticular disease	5	4	1.1 (0.3 to 4.0)	NS
Inflammatory bowel disease	8	2	3.4 (0.7 to 16.3)	NS
Bowel cancer	1	5	0.2 (0.02 to 1.5)	NS
Other	35	16	1.9 (1.1 to 3.5)	0.032
Appendectomy	67	46	1.3 (0.9 to 1.9)	NS
Tonsillectomy	116	104	1 (0.7 to 1.3)	NS

NA, not applicable; TATT, tiredness all the time.

Table 3 Gastrointestinal symptom burden in people with type 1 diabetes compared with controls

Symptoms (n)	Type 1 diabetes	Controls	OR	95% CI	P values
0	216	278	0.52	0.41 to 0.65	<0.0001
1	171	169	0.82	0.64 to 1.1	NS
2	126	77	1.49	1.09 to 2.02	0.011
3	82	41	1.80	1.22 to 2.67	0.0028
4	55	20	2.67	1.46 to 4.17	0.0005
5	40	11	3.24	1.65 to 6.37	0.00028
6	10	8	1.07	0.42 to 2.73	NS
7	6	0	–	–	0.034

People with type 1 diabetes reported constipation in 8.5% vs 3.3% in controls (OR 2.4), diarrhea in 6.1% vs 2.6% in controls (OR 2.5) and alternating bowel habit in 8.8% vs 4.5% in controls (OR 2.1). This gave a cumulative prevalence of 23.4% of such symptoms in people with type 1 diabetes compared with 10.4% for controls. Flatulence and bloating were common in both groups but significantly more so in people with type 1 diabetes. Tiredness and weight loss were also more common in people with type 1 diabetes and are often ascribed to insulin deficiency; however, the majority of individuals in this study had started insulin treatment for over a year. The only significant difference in gastrointestinal conditions from controls was a history of pancreatitis (OR 4.6) and 'other' conditions (OR 1.9). 'Other' conditions were self-reported as reflux, indigestion, *H. pylori*, hemorrhoids and previous surgery. When analyzing the prevalence of other underlying medical conditions, people with type 1 diabetes were more likely to have a history of anemia (OR 1.5), thyroid disease (OR 4.1), epilepsy (OR 4.3) and neurologic disease (OR 2.4).

Table 3 shows the symptom burden for each group, showing that people with type 1 diabetes were significantly less likely to have no gastrointestinal symptoms (OR 0.52) and that a higher proportion had a greater symptom burden compared with controls, particularly >3 symptoms.

Quality of life and glycemic control

To determine the interactions between gastrointestinal symptoms, quality of life and glycemic control, data were stratified by reported symptoms, notably constipation, diarrhea, alternating bowel habit and abdominal pain. Figure 1A–D shows the quality of life scores for each symptom group.

Constipation

Sixty individuals with type 1 diabetes described constipation as did 20 individuals from the control population. The quality of life scores were significantly worse in those with type 1 diabetes and constipation overall (all p<0.01). When comparing individuals with type 1 diabetes and constipation with those with type 1 diabetes and normal bowel habit, the quality of life scores were significantly worse in all domains except for general health perceptions and social functioning. When comparing individuals with type 1 diabetes and constipation and controls with constipation, the quality of life scores were significantly worse in all domains except for social functioning, role limitations due to emotional problems and mental health composite score. Comparing individuals with type 1 diabetes and constipation with controls with normal bowel habit, the quality of life scores were significantly worse in all domains (all p<0.01).

When comparing those with type 1 diabetes and constipation with matched individuals with type 1 diabetes and normal bowel habit, there was no significant difference in HbA1c (8.2% (66 mmol/mol) vs 7.9% (62 mmol/mol), p=0.45).

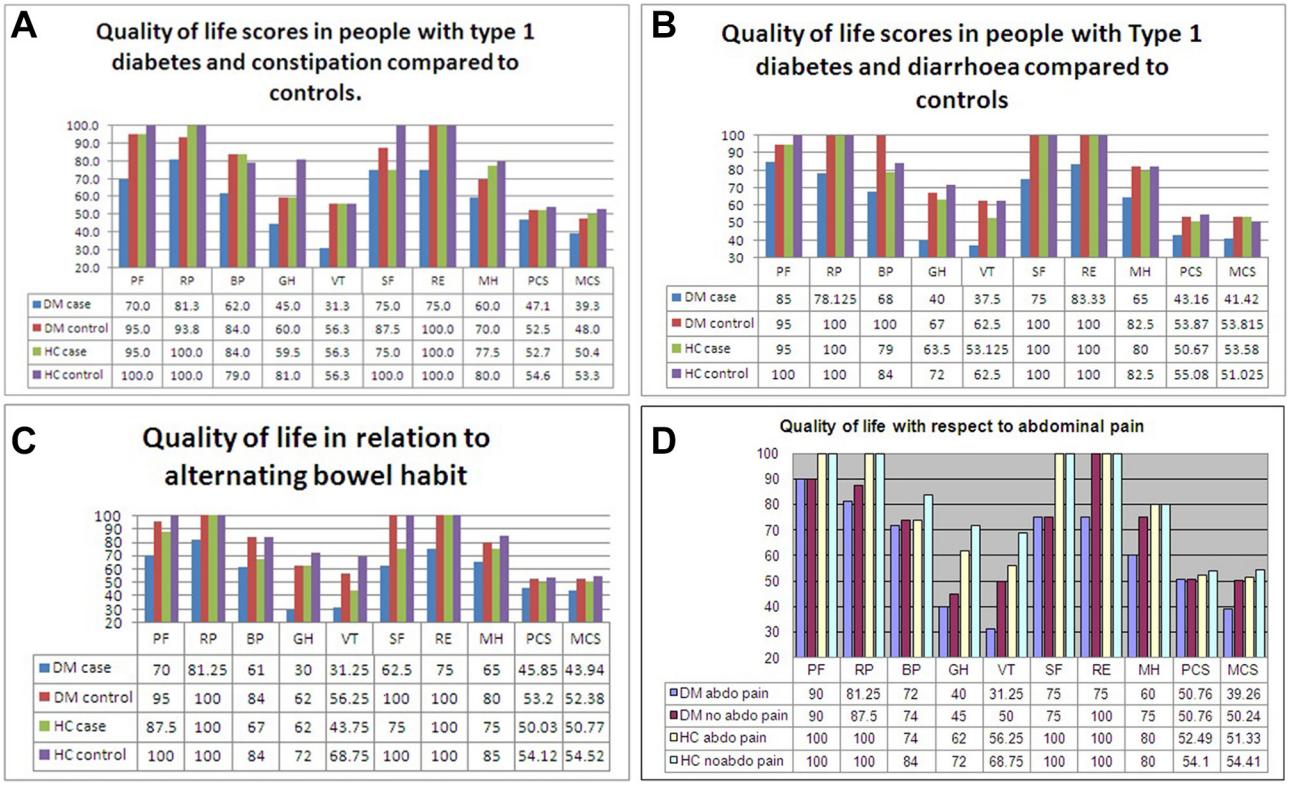
Diarrhea

Forty-three individuals with type 1 diabetes described diarrhea as did 16 individuals from the control population. Individuals with type 1 diabetes and diarrhea had significantly worse scores in all domains compared with type 1 diabetes controls with normal bowel habit. Compared with controls with diarrhea, the quality of life scores were significantly worse in all domains except for bodily pain, mental health and physical composite score. Compared with controls with normal bowel habit, the quality of life scores were significantly worse in all domains except for bodily pain.

When comparing those with type 1 diabetes and diarrhea with matched individuals with type 1 diabetes and normal bowel habit, the median HbA1c was significantly worse (8.2% (66 mmol/mol) vs 7.3% (56 mmol/mol), p<0.001).

Alternating bowel habit

Sixty-two individuals with type 1 diabetes described alternating bowel habit as did 27 individuals from the control population. Individuals with type 1 diabetes and alternating bowel habit had significantly worse scores in all domains compared with type 1 diabetes controls with normal bowel habit. Compared with controls with alternating bowel habit, the quality of life scores were



A	PF	RP	BP	GH	VT	SF	RE	MH	PCS	MCS
DM case	70.0	81.3	62.0	45.0	31.3	75.0	75.0	60.0	47.1	39.3
DM control	95.0	93.8	84.0	60.0	56.3	87.5	100.0	70.0	52.5	48.0
HC case	95.0	100.0	84.0	59.5	56.3	75.0	100.0	77.5	52.7	50.4
HC control	100.0	100.0	79.0	81.0	56.3	100.0	100.0	80.0	54.6	53.3

B	PF	RP	BP	GH	VT	SF	RE	MH	PCS	MCS
DM case	85	78.125	68	40	37.5	75	83.33	65	43.16	41.42
DM control	95	100	100	67	62.5	100	100	82.5	53.87	53.815
HC case	95	100	79	63.5	53.125	100	100	80	50.67	53.58
HC control	100	100	84	72	62.5	100	100	82.5	55.08	51.025

C	PF	RP	BP	GH	VT	SF	RE	MH	PCS	MCS
DM case	70	81.25	61	30	31.25	62.5	75	65	45.85	43.94
DM control	95	100	84	62	56.25	100	100	80	53.2	52.38
HC case	87.5	100	67	62	43.75	75	100	75	50.03	50.77
HC control	100	100	84	72	68.75	100	100	85	54.12	54.52

D	PF	RP	BP	GH	VT	SF	RE	MH	PCS	MCS
DM abdo pain	90	81.25	72	40	31.25	75	75	60	50.76	39.26
DM no abdo pain	90	87.5	74	45	50	75	100	75	50.76	50.24
HC abdo pain	100	100	74	62	56.25	100	100	80	52.49	51.33
HC noabdo pain	100	100	84	72	68.75	100	100	80	54.1	54.41

Figure 1 (A) Quality of life scores in individuals with and without constipation. (B) Quality of life scores in individuals with and without diarrhea. (C) Quality of life scores in individuals with and without alternating bowel habit. (D) Quality of life scores in individuals with and without abdominal pain. BP, bodily pain; DM, diabetes mellitus; GH, general health perceptions; HC, healthy control; MCS, mental health composite score; MH, mental health; PCS, physical composite score; PF, physical functioning; RE, role limitations due to emotional problems; RP, role limitations due to physical health; SF, social functioning; VT, vitality.

significantly worse in all domains except for bodily pain and physical composite score. Compared with controls with normal bowel habit, the quality of life scores were significantly worse in all domains. When comparing those with type 1 diabetes and alternating bowel habit with matched individuals with type 1 diabetes and normal bowel habit, the median HbA1c was significantly worse (8.5% (69 mmol/mol) vs 7.9% (62 mmol/mol), p=<0.001).

Abdominal pain

One hundred and twenty-six individuals with type 1 diabetes described abdominal pain as did 81 individuals from the control population. Individuals with type 1 diabetes and abdominal pain had significantly worse scores only in the role limitations due to emotional problems, mental health and mental health composite score domains compared with type 1 diabetes controls without abdominal pain. Compared with controls with abdominal pain, the quality of life scores were significantly worse in all domains except for bodily pain. Compared with controls without abdominal pain, the quality of life scores were significantly worse in all domains.

When comparing those with type 1 diabetes and abdominal pain with matched individuals with type 1 diabetes without abdominal pain, the median HbA1c was significantly worse (8.25% (67 mmol/mol) vs 7.7% (61 mmol/mol), p=0.0021).

Diabetes-related complications

The gastrointestinal questionnaire specifically asked about known complications of diabetes, including retinopathy, nephropathy, neuropathy, arthropathy and gastric problems. Overall, 249 (35.3%) had retinopathy, 55 (7.8%) had nephropathy, 133 (18.8%) had neuropathy, 82 (11.6%) had arthropathy and 35 (4.9%) had gastric problems.

To assess whether gastrointestinal symptoms were associated with more complications of diabetes, comparison was made between frequencies of each complication stratified by symptom type. In those with normal bowel habit (n=515), the frequency of retinopathy, nephropathy, arthropathy, neuropathy and gastric problems was 32.6%, 6.0%, 9.5%, 15% and 1.7%, respectively.

Neuropathy was significantly more common in people with type 1 diabetes and any change in bowel habit. Retinopathy was associated with diarrhea and alternating bowel habit but not constipation or abdominal pain. Nephropathy was associated with diarrhea and alternating bowel habit but not constipation or abdominal pain. Joint problems were associated with diarrhea and alternating bowel habit but not constipation or

Table 4 Final diagnoses in those individuals with type 1 diabetes and diarrhea

Diagnosis	n (%)
Irritable bowel syndrome	34 (36.2)
Autonomic neuropathy	14 (14.9)*
Inflammatory bowel disease	10 (10.6)†
Celiac disease	9 (9.6)
Exocrine pancreatic disease	6 (6.4)‡
Small bowel bacterial overgrowth	5 (5.3)
Lactose intolerance	1 (1.1)
IgA deficiency	1 (1.1)
Diverticular disease	1 (1.1)
Peritoneal dialysis-related	1 (1.1)
Rectal cancer	1 (1.1)
Unclassified	11 (11.7)

*5 individuals had small bowel bacterial overgrowth on glucose hydrogen breath testing.
†7 ulcerative colitis, 2 Crohn's disease and 1 microscopic colitis.
‡2 individuals had calcific pancreatitis on CT scanning (2 individuals had celiac disease and chronic pancreatitis, 2 individuals had celiac disease and inflammatory bowel disease, and 1 individual had celiac disease and autonomic neuropathy).

abdominal pain. Gastric problems were associated with all bowel habit changes but most strongly with diarrhea.

Investigations

One hundred and five individuals with type 1 diabetes had diarrhea as a component of their symptoms (62 with alternating bowel habit and 43 with diarrhea) and were contacted and offered further investigations. Of these 94 (92.2%) were willing to undergo the investigations as described in the Research design and methods section. The other 11 were either unwilling to be investigated or did not consider their symptoms significant enough to undergo the proposed investigations. Table 4 shows the final diagnoses in this group following investigations.

Following assessment and investigation, 34/94 (36.2%, 26.5–46.7) met the Rome III criteria for irritable bowel syndrome and were treated with antispasmodics and/or low-dose antidepressants. Fourteen of 94 (14.9%, 8.4–23.7) had autonomic neuropathy (5 of whom also had small bowel bacterial overgrowth and improved with antibiotics). Fourteen of 94 had positive celiac serology, of whom 9 had villous atrophy on biopsy (9.6%, 4.5–17.4) and commenced a gluten-free diet. Ten of 94 (10.6%, 5.2–18.7) had inflammatory bowel disease (7 ulcerative colitis, 2 Crohn's disease and 1 microscopic colitis) and were started on treatment. Six individuals had exocrine pancreatic disease (two with chronic pancreatitis on CT scan), all of whom improved on enzyme supplements. Overall, there was a change in management in 68/94 (72.3%).

DISCUSSION

This is the largest study of gastrointestinal symptoms in people with type 1 diabetes, in particular lower intestinal symptoms. Overall, people with type 1 diabetes were almost twice as likely to describe gastrointestinal symptoms compared with controls, with about one in four (23.4%) describing constipation, diarrhea, or alternating bowel habit. Furthermore, symptom burden was significantly higher compared with controls. Further analysis showed that diarrhea, constipation or alternating bowel habits were significantly more common compared with controls, as were symptoms such as flatulence and bloating, and were associated with poorer quality of life scores. Glycemic control was also significantly worse in those with diarrhea, abdominal pain or alternating bowel habits. Despite these symptoms, only a history of pancreatitis was significantly more common when comparing known gastrointestinal conditions. This may explain the constellation of abdominal pain, diarrhea, floating stools and weight loss, which could be attributed to exocrine pancreatic disease. Indeed, following investigation, 6.4% of people with type 1 diabetes and diarrhea were found to have exocrine pancreatic disease, including two individuals with calcific pancreatitis. Both of whom had a history of significant alcohol intake for many years.

A further interesting finding was that gastrointestinal symptoms were associated with increased risk of diabetes-related complications. Neuropathy and stomach problems were associated with any change in bowel habit, whereas diarrhea or alternating bowel habits were associated with increased risk of all diabetes-related complications. These findings are similar to the initial description of *diabetic diarrhea* by Bargen,[4] in which peripheral neuropathy was frequently associated.

The association between gastrointestinal symptoms and poor glycemic control leads to a 'chicken and egg' hypothesis. From our data it is impossible to determine whether gastrointestinal symptoms lead to poor glycemic control, or whether poor glycemic control leads to gastrointestinal symptoms.

Importantly this study detected underlying gastrointestinal disorders in those with diarrhea. To date there are no published data examining the findings of investigations for diarrhea in a large cohort of people with type 1 diabetes. Irritable bowel syndrome accounted for around one-third of all people investigated, with autonomic neuropathy being the second most common positive finding. Not all of those with autonomic neuropathy had small bowel bacterial overgrowth according to glucose hydrogen breath testing, but this may represent false-negative results.[31] Additionally, autonomic function was tested using cardiac function rather than intestinal motility or manometry studies. The correlation between cardiac autonomic dysfunction and intestinal autonomic dysfunction is not 100%.[32 33] The finding of a high prevalence of inflammatory bowel disease is novel and has been confirmed in a recent study.[34]

Exocrine pancreatic disease is not unexpected and suggests that some people with diabetes may have been misclassified. A previous study by Hardt *et al*[35] showed that around 10% of patients with type 1 or type 2 diabetes may actually have type 3c diabetes.[28] The hypothesis is that patients present with diabetes-related symptoms for which they are treated, but they may have only subtle exocrine symptoms. Identification of these individuals is likely to be important as other therapies may be required, such as pancreatic enzyme supplementation.[35] Furthermore, some of the newer medications such as the incretins may be more suitable for people with type 3c diabetes.

The frequency of some of the conditions identified initially appears questionable with high prevalence of both celiac disease and inflammatory bowel disease and low prevalence of lactose intolerance. However, all of these individuals had assessment for celiac disease and underwent colonoscopy, but assessment for lactose intolerance was not a first-line investigation, which would have reduced the overall prevalence. If an individual had a positive finding on the initial set of investigations, then further tests were not conducted.

The other diagnoses were expected except the finding of a rectal cancer. This individual was an older man who had started with looser motions over the previous few months. Colonoscopy revealed a significant lesion in the mid-rectum, which went on to be completely resected. A previous meta-analysis has shown that diabetes is a risk factor for colorectal cancer possibly due to hyperinsulinemia[36] but is also associated with adverse outcomes following surgery for colorectal cancer.[37] Our data suggest that diarrheal symptoms in people with type 1 diabetes deserve investigation before being ascribed nihilistically to autonomic neuropathy.

Despite this being such a large study with a suitable control group, there are a number of unanswered questions. This study was an epidemiologic study and not designed to establish mechanisms by which people with type 1 diabetes acquire gastrointestinal symptoms. Many of these symptoms were self-reported and not attributed to a formal diagnosis following investigations, for example, gastric problems. The focus of this study was however lower gastrointestinal symptoms. Despite this, the prevalence of gastrointestinal symptoms in the control group is in keeping with that of previous population-based studies.[5] The prevalence of underlying diagnoses was not compared with that in the control group as these individuals were not investigated and 11 individuals with type 1 diabetes declined investigations. However, this represents less than 10% of those with type 1 diabetes and diarrhea and may represent symptom cycling.[8] Additionally, initial assessment did not take prescribed medications into account, which may be a confounder. In those undergoing further assessment for diarrhea, a full medication history was taken but were not felt to account for any gastrointestinal symptoms. Most of the cohort were young and not on other medications other than insulin. Several conclusions can be drawn in this regard as the prevalence of irritable bowel syndrome in the general population is known to be approximately 15%. Our data support the theory that people with type 1 diabetes may perceive gastrointestinal symptoms more readily than people without diabetes suggested by the greater prevalence of gastrointestinal symptoms, including flatulence and bloating, as well as the increased prevalence of irritable bowel syndrome. Whether this is due to subtle changes in the autonomic nervous system or other intestinal hormones remains unclear. Previous studies have demonstrated that glycemic control has an effect on gastric function,[15–19] but there are little data on lower gastrointestinal function. Confounding factors in previous studies have been the lack of investigation for underlying conditions, no face-to-face assessments and self-reporting of glycemic control.[5 6] Additionally, previous studies have not assessed quality of life and, importantly, have not had a control group.

In conclusion, we have shown for the first time that lower gastrointestinal symptoms are common in type 1 diabetes and have a significant effect on the quality of life and glycemic control. Investigation of patients with diarrhea had a high yield of treatable conditions, and therefore care for people with diabetes should encompass gastrointestinal assessments routinely.

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Contributors JSL and DSS conceived and designed the study. JSL, MH, ST and DSS acquired, analyzed and interpreted the data. JSL and DSS drafted the manuscript. JSL, MH, ST and DSS critically revised the manuscript for important intellectual content. JSL and DSS performed the statistical analysis. DSS and JSL obtained funding. MH, ST and DSS provided technical and material support. MH, ST and DSS provided study supervision. All authors had access to the study data and have reviewed and approved the final manuscript. DSS is the guarantor for the study.

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