Prevalence of Gastrointestinal Symptoms Associated With Diabetes Mellitus

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Background: Gastrointestinal symptoms are reportedly common in diabetes, but a causal link is controversial and adequate population control data are lacking.

Objective: To determine whether gastrointestinal symptoms are more frequent in persons with diabetes, particularly in those with poor glycemic control.

Methods: Fifteen thousand adults were mailed a questionnaire (response rate, 60.0%) containing validated questions on the frequency of troublesome gastrointestinal symptoms within the past 3 months, diabetic status, and self-reported glycemic control. The prevalence of 16 symptoms and 5 symptom complexes, reported to occur often or very often, was compared using logistic regression analysis, adjusting for age and sex.

Results: Overall, 8657 eligible subjects responded; 423 (4.9%) reported having diabetes. Most (94.8%) had type 2 diabetes mellitus. Adjusting for age and sex, all 16 symptoms and the 5 symptom complexes were significantly more frequent in subjects with diabetes compared with controls. An increased prevalence rate of symptoms was significantly associated with poorer levels of glycemic control but not with duration of diabetes or type of diabetic treatment.

Conclusions: Diabetes mellitus is associated with an increased prevalence of upper and lower gastrointestinal symptoms. This effect may be linked to poor glycemic control but not to duration of diabetes or type of treatment.


Gastrointestinal (GI) symptoms are reportedly common in diabetes mellitus and are usually attributed to autonomic neuropathy. Although there is evidence that GI symptoms affect quality of life adversely and represent a substantial cause of morbidity in patients with diabetes, the available epidemiological data relating to the prevalence of GI symptoms in diabetes are conflicting and can be challenged on methodological grounds.

Recently, Schvarcz et al evaluated the prevalence of GI symptoms in a nonselected, population-based cohort of 110 young adult patients with long-standing type 1 diabetes mellitus, compared with age- and sex-matched control subjects. In the patients with diabetes, there was an increased prevalence of upper GI symptoms, such as anorexia and vomiting, whereas there was no difference in the frequency of symptoms referable to the lower GI tract. The prevalence of GI symptoms was significantly greater in women than in men and in those subjects with the worst glycemic control, as assessed by glycated hemoglobin concentrations. On the other hand, Janatuinen et al found that the prevalence of upper GI symptoms, abdominal pain, constipation, and diarrhea was similar in patients with diabetes and controls. In that study, only middle-aged patients with type 1 or type 2 diabetes mellitus who were treated with insulin or oral hypoglycemic drugs were evaluated, and the questionnaire used to evaluate symptoms was not a validated measure. A recent study from Hong Kong reported higher rates of all types of GI symptoms in 149 patients with type 2 diabetes mellitus who were referred to a university clinic, compared with community controls. In this study, the duration of diabetes was the only factor independently associated with GI symptoms. A German study of 333 diabetic patients referred to a diabetes research institute found that only patients with type 2 diabetes mellitus had more upper and lower GI symptoms than did community controls, the most common symptom being constipation. Finally, a recent community-based study from the United States failed to detect differences in prevalence rates for GI tract symptoms in persons with or without diabetes.
MATERIALS AND METHODS

SURVEY METHOD

In Australia, all adults aged 18 years and older are required by law to be registered on the electoral rolls. Fifteen thousand subjects on the electoral rolls for Penrith and the Blue Mountains areas west of Sydney, Australia, were randomly selected for the study. This area has a population of 155,000, which is demographically similar to the general Australian population, according to the 1996 census data, except that it is slightly younger and of slightly higher socioeconomic status.11

The survey was conducted from August 1, 1999, to September 15, 1999, and the study was closed at the end of November 1999. The list of selected subjects was divided into 5 batches of 3000 subjects each, and mailings were begun at intervals approximately 1 week apart. A letter outlining the study and requesting their participation was sent to all eligible subjects. A $2.00 lottery ticket was included to enhance the response rate.24 Subjects were given the option of refusing to participate. Two reminder letters were sent at 3-week intervals. Ethical approval was obtained from the Wentworth Area Health Service Research and Ethics Committee of Nepean Hospital, Penrith.

ASSESSMENT OF SYMPTOMS

The 2-page questionnaire was based on elements from questionnaires that have previously been validated.15-24 Individual questions were taken from the Bowel Disease Questionnaire,25 and the period was adapted from the validated questionnaire by Agerus et al.27 The questionnaire contained 16 questions on the frequency of GI symptoms that had been troublesome in the preceding 3 months. The frequency of each symptom was rated on a 5-point Likert scale and coded as not at all, rarely, sometimes, often, or very often. For the purposes of this analysis, a positive answer was recorded when the troublesome symptom was reported to occur often or very often.

All symptoms that were not completely self-explanatory were accompanied by a standard description, consistent with the Rome II criteria.6,28 early satiety (feeling full soon after starting to eat, rendering the person unable to finish a normal meal); postprandial fullness (an unpleasant feeling of food staying in the stomach after a normal meal); bloating (a feeling as if the stomach or abdomen were swollen); heartburn (a burning pain or discomfort behind the breastbone rising up toward the throat); dysphagia (difficulty in swallowing, in which solid food or liquids stick on the way down); an anal blockage (a feeling of blockage in the anus or back passage that made it difficult to pass bowel movements); and urgency (a need to have a bowel movement that made the person rush to the toilet).

Subjects were classified into the following 5 symptom complexes based on their symptoms reported to occur often or very often: esophageal symptoms (heartburn, dysphagia, or both); upper dysmotility symptoms (any of the symptoms of early satiety, postprandial fullness, bloating, nausea, or vomiting); any bowel symptom (any of the symptoms of self-reported diarrhea or constipation, loose or watery stools, ≥3 bowel movements per day, urgency, fecal incontinence, <3 bowel movements per week, lumpy or hard stools, or anal blockage); diarrhea symptoms (any of the symptoms of ≥3 bowel movements per day, loose or...
of the community was expected to range from approximately 2% to 15%. An elevation among subjects with diabetes of 10% was deemed to be the least that would be of clinical significance. To achieve a statistical power of 0.9 at the P<.05 level of statistical significance, 120 subjects would be required per study group for symptoms with a prevalence in the community of 2%, while 335 would be required per study group for symptoms with a prevalence of 15%. To determine how many subjects would need to be surveyed by mail to obtain 335 subjects with diabetes with usable data, it was assumed that the prevalence of known diabetes in the community was 4% 21 and that a response rate of 70% would be achieved. 23 The calculations suggested that a mailing of approximately 12,000 would be required. This was increased to 15,000, because resources allowed for it and in case the response rate was lower than expected.

The association between diabetes and the proportion of subjects with and without poor glycemic control, logistic regression models were developed. A forward stepwise analysis was used to identify which symptoms or symptom groups independently differentiated the groups, after adjusting for confounding factors.

Of 15,000 questionnaires mailed, 429 were returned because the address was unknown or incorrect. Another 99 persons did not receive their questionnaires; this group consisted mostly of people who had died recently or who were overseas. Six hundred twenty-three people refused to participate and returned the questionnaire blank. Of the 14,472 that were delivered, 8,657 questionnaires were completed and returned, for a response rate of 60.0%. The mean ± SD age of the respondents was 45.3 ± 15.8 years (range, 18-101 years), and the proportion of respondents who were 40 years and older was similar to that of the Australian adult population in general (61.8% vs 61.0%). The proportion of women in the responding sample was slightly higher compared with that of the Australian population (53.5% vs 51.4%).

Four hundred seventy-two subjects (5.4%) reported having diabetes. Of these, 49 women reported diabetes in pregnancy only, leaving 423 subjects with diabetes (4.9%) for further analysis.

Subjects with diabetes were older than controls (59.5 ± 14.1 years vs 44.6 ± 15.6 years, P < .001) and more women were treated with insulin (23.4% vs 15.7%, P = .08). Three hundred sixty-two subjects (85.6%) with diabetes were 45 years and older. Therefore, these differences were adjusted for in the logistic regression analyses.

Table 1 summarizes characteristics of the subjects with diabetes. The mean duration of known diabetes was 5.0 years (interquartile [IQ] range, 2.2-11.0 years). Most (94.8%) of the patients had type 2 diabetes mellitus and were receiving oral hypoglycemic therapy. There was no sex variation in type of diabetes, levels of self-reported glycemic control, or duration of disease. There was a trend for more women to be treated with insulin compared with men (23.4% vs 15.7%, P = .08).

Patients with diabetes reported significantly more symptoms per individual than control subjects (1.39, IQ range, 0-2 vs 0.96, IQ range, 0-1; P < .001). No symp-
pared with only 3.8% of the controls (423 subjects with diabetes at least sometimes, com-
fecal incontinence (OR, 2.74; 95% CI, 1.40-5.37), dys-
age and sex. The strongest associations were found for
symptoms and each of the 5 symptom groups had a sig-
nificantly higher prevalence among persons with diabe-
tics, and only 6 (4.3%) reported 6 or more symptoms.

Table 1. Characteristics of 423 Diabetic Subjects*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (SD), y</td>
<td>59.5 (14.1)</td>
</tr>
<tr>
<td>Male:female, No.</td>
<td>229:194</td>
</tr>
<tr>
<td>Type 1 diabetes mellitus</td>
<td>22 (5.2)</td>
</tr>
<tr>
<td>Diabetes treatment</td>
<td></td>
</tr>
<tr>
<td>Insulin only</td>
<td>45 (10.6)</td>
</tr>
<tr>
<td>Insulin and tablets</td>
<td>32 (7.6)</td>
</tr>
<tr>
<td>Tablets only</td>
<td>198 (46.8)</td>
</tr>
<tr>
<td>Diet only</td>
<td>125 (29.6)</td>
</tr>
<tr>
<td>No data</td>
<td>23 (5.4)</td>
</tr>
<tr>
<td>Duration of known diabetes, y</td>
<td></td>
</tr>
<tr>
<td>&lt;5</td>
<td>183 (43.3)</td>
</tr>
<tr>
<td>5-10</td>
<td>85 (20.1)</td>
</tr>
<tr>
<td>&gt;10</td>
<td>124 (29.3)</td>
</tr>
<tr>
<td>No data</td>
<td>31 (7.3)</td>
</tr>
<tr>
<td>Glycemic control</td>
<td></td>
</tr>
<tr>
<td>Very good</td>
<td>88 (20.8)</td>
</tr>
<tr>
<td>Good</td>
<td>141 (33.3)</td>
</tr>
<tr>
<td>Average</td>
<td>143 (33.8)</td>
</tr>
<tr>
<td>Poor</td>
<td>32 (7.6)</td>
</tr>
<tr>
<td>Very poor</td>
<td>5 (1.2)</td>
</tr>
<tr>
<td>No data</td>
<td>14 (3.3)</td>
</tr>
</tbody>
</table>

*Data are given as number (percentage) unless otherwise indicated.

Glycemic control

Overall, 37 subjects with diabetes rated their glycemic control as poor or very poor, compared with 229 subjects who rated their control as good or very good; 143 subjects rated their glycemic control as average (Table 1). There was a dose-response relationship between the quality of self-reported glycemic control and the prevalence rates of all symptoms (except for early satiety and fecal incontinence), with higher prevalence rates associated with poorer levels of glycemic control (Table 3). After adjusting for age and sex, there was an association between poor glycemic control and the 5 symptom complexes, and a moderate to strong association with 12 of the 16 symptoms (Table 3). For 4 of the symptoms (early satiety, vomiting, <3 bowel movements per week, and loose or watery stools), the association failed to reach statistical significance, but there was a clear trend in the direction of self-reported poor control (Table 3).

Adjusting for the confounding factors of age and sex, the symptoms lumpy or hard stools (OR, 3.75; 95% CI, 1.72-8.17) and urgency (OR, 3.12; 95% CI, 1.55-6.26) and the symptom complex upper dysmotility symptoms (OR, 1.97; 95% CI, 1.16-3.37) were independently associated with self-reported poor glycemic control.

Patients with diabetes who reported poor glycemic control had significantly more symptoms per individual compared than patients with average glycemic control (3.49, IQ range, 0-6 vs 1.38, IQ range, 0-2; P < .001) or patients with good glycemic control (3.49, IQ range, 0-6 vs 0.89, IQ range, 0-1; P < .001). Of 37 patients with poor control, 11 (29.7%) reported no symptoms and 7 (18.9%) reported 6 or more symptoms. The corresponding figures for 143 patients with average glycemic control were 77 (53.8%) and 13 (9.1%). Of 141 patients with good glycemic control, 96 (68.1%) did not report any symptoms and only 6 (4.3%) reported 6 or more symptoms.

Duration of diabetes was not significantly associated with the prevalence of GI symptoms. After adjusting for age, sex, and self-reported glycemic control, only the symptom complex constipation (OR, 2.46; 95% CI, 1.32-4.56) and the symptoms anal blockage (OR, 2.28; 95% CI, 1.12-4.67) and lumpy or hard stools (OR, 2.45; 95% CI, 1.14-5.27) were significantly associated with long-standing diabetes. In a median regression analysis, patients with constipation reported a disease duration on average 2.1 years longer (95% CI, 0.17-5.33; P < .04) than patients without that symptom complex.

Type of diabetes

Patients with type 1 diabetes mellitus tended to have fewer GI symptoms than those with type 2 diabetes, after adjusting for age, sex, and self-reported glycemic control. However, only the symptom complex any bowel symptom was significantly more common in subjects with type 2 diabetes in an adjusted model (OR, 8.33; 95% CI, 1.39-50.0).

Type of diabetes treatment

We undertook 3 different analyses to explore any association between types of diabetes treatment and prevalence of GI symptoms. In these analyses, adjustments were made for age, sex, and self-reported glycemic control. In the first analysis, 77 patients who were insulin users were compared with 323 non-insulin users. We found no significant differences in the prevalence of any symptom or symptom complex. In the second analysis, 198 users of oral hypoglycemic drugs were compared with 170 patients who did not use these drugs. Only anal blockage was significantly less common in oral hypoglycemic drug
users (OR, 0.38; 95% CI, 0.16-0.88). In the final analysis, 125 patients who were treated with diet only were compared with 275 users of insulin, oral hypoglycemic drugs, or both. Postprandial fullness (OR, 2.29; 95% CI, 1.10-4.77), anal blockage (OR, 2.84; 95% CI, 1.29-6.24), and the symptom complex constipation (OR, 2.09; 95% CI, 1.07-4.08) were significantly more common in patients treated with diet only.

We used a standard questionnaire and applied well-accepted criteria to diagnose diabetes mellitus in community subjects. Compared with data reported from a population-based US study, using the same criteria for diagnosis and type of diabetes, we found nearly identical prevalence rates of subjects with known diabetes in the community (4.4% vs 4.9%), proportion of type 1 diabetes mellitus (7% vs 5.2%), and proportion of subjects with diabetes aged 45 years and older (83% vs 86%). The prevalence of diabetes, including gestational diabetes, was only slightly higher in our study (5.4%) compared with the estimates given in a recent health survey in our area, because, according to epidemiological data, the possibility that persons with diabetes may have been more likely to return the questionnaire than nondiabetic subjects, it is unlikely that any response bias would have seriously affected the results of the study. It is also unlikely that subjects with undiagnosed diabetes mellitus among the control subjects would have skewed the results, because, according to epidemiological data, the prevalence of undiagnosed diabetes in adults in Australia is only around 2%.32

The present study had important methodological strengths. We designed the survey to have sufficient power to detect differences in prevalence rates of 10% or more.
The pathogenesis of GI symptoms in diabetes has not been clearly elucidated. It has been suggested that neurological impairment, especially autonomic neuropathy, is an important factor. However, other investigators have observed a poor correlation between GI symptoms and autonomic neuropathy, although in most studies the latter has been evaluated using standardized cardiovascular reflexes, rather than a specific test of GI autonomic function. Furthermore, patients with diabetes without demonstrable neuropathy also experience GI symptoms and autonomic neuropathy, although in most studies the latter has been evaluated using standardized cardiovascular reflexes, rather than a specific test of GI autonomic function. Furthermore, patients with diabetes without demonstrable neuropathy also experience GI symptoms and autonomic neuropathy, although in most studies the latter has been evaluated using standardized cardiovascular reflexes, rather than a specific test of GI autonomic function. 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are consistent with those of 2 other studies\textsuperscript{13,38} in which diarrhea was reported to be associated with metformin treatment, but not with diet control, insulin use, or treatment with other types of oral hypoglycemic drugs. In this study, we did not obtain information on specific types of oral hypoglycemic drugs used.

Our results demonstrate that self-reported poor glycemic control is strongly associated with presence of GI symptoms. We found a dose-response relationship between the level of self-reported glycemic control and the prevalence rates of the 5 symptom complexes and 12 of the 16 symptoms, with higher prevalence rates associated with poorer glycemic control. The plausibility of the results is supported by the findings of several physiological studies\textsuperscript{15,22,23,30-41} in healthy controls and in patients with diabetes that have established that acute hyperglycemia affects GI motor function and the perception of sensations arising from the GI tract. For example, the perception of nausea, occurring as a result of proximal gastric distension, is greater during hyperglycemia.\textsuperscript{14} Acute hyperglycemia also slows gastric emptying in persons with diabetes,\textsuperscript{42} reduces lower esophageal sphincter pressure and the velocity of esophageal peristalsis,\textsuperscript{39} and alters motility in the small bowel and gallbladder.\textsuperscript{41} The gastrocolic and ascending components of the colonic peristaltic reflex are inhibited during hyperglycemia in healthy subjects,\textsuperscript{35} but colonic tone, compliance, and motor patterns were not affected in another study.\textsuperscript{45}

Although a direct measure of glycemic control would have been preferable, this was not possible in our epidemiological study. However, investigators have recently shown that self-reported glycemic control, using a 5-point scale similar to ours, was significantly correlated with objective measures of glycemic control, including glycated hemoglobin ($P<.001$) and plasma glucose ($P=.005$) levels in 166 subjects with diabetes (N.J.T., Johann Hammer, MD, M.P.J., and M.H., unpublished data, February 1999). No specific guidelines were offered to the patients in the present study about which category average blood glucose level would correspond to among the various categories of self-reported glycemic control. It is therefore possible that many patients underestimated their level of good glycemic control. However, this bias toward optimism would tend to strengthen the present observations.

Unfortunately, the direction of the association between poor glycemic control and GI symptoms could not be addressed by the methods used in this study. Symptoms of upper GI dysmotility, including nausea, vomiting, and early satiety, may lead to loss of glycemic control as a result of unpredictable delivery of nutrients to the small intestine. Therefore, we cannot exclude the possibility that upper GI symptoms, secondary in part to autonomic neuropathy, have led to poor glycemic control. However, this hypothesis would not explain the increased prevalence of symptoms related to bowel dysfunction, such as constipation, diarrhea, urgency, and fecal incontinence. A logical extension of this work will be to undertake longitudinal studies to establish the direction of these associations and to differentiate causes from effects. However, as previously stated, several pathophysiological studies\textsuperscript{15,30-42} suggest that poor glycemic control in itself promotes symptoms arising from all parts of the GI tract.

We were also unable to measure other risk factors that may be important in the pathogenesis of GI symptoms in diabetes, such as diabetic complications, psychosocial distress or psychiatric comorbidity, alcohol ingestion, obesity, and the use of medications other than insulin and oral hypoglycemic agents. Patients with type 2 diabetes mellitus are characteristically obese, and obesity is a risk factor for dyspepsia (broadly defined) in women,\textsuperscript{44} but a role for obesity in other GI symptoms remains uncertain. The relative importance of the type of diabetes could not be evaluated definitively because only 22 subjects had established type 1 diabetes mellitus.

In summary, this population-based study provides evidence that troublesome GI symptoms are more prevalent in subjects with diabetes compared with controls, especially in those who report poor glycemic control. Our findings suggest that this effect may be explained, at least in part, by poor glycemic control and is not associated with duration of diabetes or type of diabetic treatment.

Accepted for publication January 9, 2001.

This work was supported by grants from Diabetes Australia, Sydney, and the National Health and Medical Research Council of Australia, Canberra (grant 980080).

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