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# Epidemiology of Disordered Gastrointestinal Function and Impact of Chronic Gastrointestinal Symptoms on Quality of Life

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## Introduction

Patients with diabetes mellitus commonly complain of gastrointestinal symptoms, including chronic abdominal pain and bowel dysfunction, for which there is no structural cause [1–11]. It is now widely recognised, although only relatively recently, that complications involving the gastrointestinal tract represent an important cause of morbidity in patients with diabetes

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mellitus [12,13]. However, epidemiological studies of these problems remain sparse and the data are conflicting. In addition, aspects of quality of life have attracted increased interest in the past few years, as it has been shown that gastrointestinal problems can impair well-being and daily life in diabetes.

## Epidemiology of gastrointestinal symptoms in diabetes

### Prevalence of gastrointestinal symptoms in diabetes mellitus

Several studies have aimed to evaluate the frequency of gastrointestinal symptoms in patients with non-insulin-dependent and insulin-dependent diabetes, but at present no uniform picture can be drawn from these results. An enormous range in the prevalence of gastrointestinal symptoms has been identified in these studies. This probably relates in part to the methodology applied and the types of populations studied (Table 1.1). Although gastrointestinal symptoms were usually assessed by either interview or standard questionnaire, the criteria applied to identify relevant symptoms differed between the studies. Few studies compared symptoms in diabetic patients with adequately matched controls. Moreover potential confounders, such as the duration of disease, glycaemic control and the presence or absence of autonomic neuropathy or psychiatric disorders, were not corrected for in most of the studies.

An ideal study of the epidemiology of gastrointestinal symptoms needs to take into account a number of issues specific to patients with diabetes. An unselected sample of the diabetes population should be compared to an appropriately matched control population. The control group for population-based studies should be selected at random from the healthy population. However, for outpatient studies disease controls are usually more appropriate than healthy controls because the selection forces differ in the clinic [14]. The populations studied need to be carefully characterised, including by age and sex, type and duration of diabetes, type and success of therapy, the presence or absence of diabetic complications, and the type of complications. It is of particular importance that symptoms are assessed by adequately validated measures. However, although validated measures that evaluate gastrointestinal symptoms exist for a variety of diseases, no diabetes mellitus-specific questionnaire has been widely available. Recently, a disease-specific questionnaire, the Diabetes Bowel Symptom Questionnaire (DBSQ), has been developed for use in both epidemiological and clinical studies of patients with diabetes. The items included in this questionnaire assess both gastrointestinal symptoms in diabetes as well as diabetic disease status, and the instrument appears to be reliable and valid [11].

### Outpatient studies of gastrointestinal symptoms in diabetes mellitus

The early literature emphasised the high prevalence of gastrointestinal symptoms in patients with diabetes complicated by neuropathy [15,16]. More than six

**Table 1.1** Outpatient studies and population-based studies assessing gastrointestinal symptoms in diabetic patients

| Reference | Population studied | Size of study population | Number of patients studied | Type of diabetes | Interview-based assessment | Questionnaire-based assessment | Control subjects studied | Patients with any gastrointestinal symptoms (%) |
|---|---|---|---|---|---|---|---|---|
| Dandona *et al.*, 1983 [20] | Outpatients | N/A | 285 | NIDDM and IDDM ($n = ?$) ($n = ?$) | NO | Not validated questionnaire | YES | 19% |
| Feldman and Schiller, 1983, [4] | Outpatients | N/A | 136 | NIDDM and IDDM ($n = ?$) ($n = ?$) | YES | N/A | NO | 76% |
| Clouse and Lustmann, 1989 [17] | Outpatients | N/A | 114 | NIDDM and IDDM ($n = 57$) ($n = 75$) | YES | N/A | NO | 68% |
| Maxton and Whorwell, 1991 [19] | Outpatients | N/A | 200 | NIDDM and IDDM ($n = ?$) ($n = ?$) | YES | N/A | YES | Not stated |
| Keshavarzian and Iber, 1987 [21] | Outpatients | N/A | 75 | IDDM ($n = 75$) | YES | N/A | NO | 19% |
| Maser *et al.*, 1990 [22] | Outpatients | N/A | 168 | IDDM ($n = 168$) | YES | N/A | NO | Not stated |
| Enck *et al.*, 1994 [23] | Outpatients | N/A | 190 | NIDDM and IDDM ($n = 68$) ($n = 75$) | NO | Not validated questionnaire | YES | Not stated |
| Ko *et al.*, 1999, [18] | Outpatients | N/A | 149 | NIDDM ($n = 149$) | NO | Not validated questionnaire | YES | 71% |
| Dyck *et al.*, 1993 [24] | General population | 870 | 380 | NIDDM and IDDM ($n = 278$) ($n = 102$) | YES | N/A | NO | Not stated |
| Schvarcz *et al.*, 1995 [25] | General population | 125 | 110 | IDDM ($n = 110$) | NO | Validated questionnaire | YES | Not stated |
| Janatuinen *et al.*, 1993 [26] | General population | 624 | 538 | NIDDM and IDDM ($n = 451$) ($n = 87$) | NO | Not validated questionnaire | YES | Not stated |
| Spångeus *et al.*, 1999 [27] | General population | 489 | 261 | NIDDM and IDDM ($n = 61$) ($n = 200$) | NO | Validated questionnaire | YES | Not stated |
| Ricci *et al.*, 2000 [28] | General population | ? | 483 | NIDDM and IDDM ($n = 61$) ($n = 200$) | YES | N/A | YES | 50% |
| Maleki *et al.*, 2000 [29] | General population | ? | ? | NIDDM and IDDM ($n = 217$) ($n = 138$) | NO | Validated questionnaire | YES | Not stated |
| Hammer [30] | | | | | | | | |
| Bytzer *et al.*, 2000 [31] | General population | 15 000 | 423 | NIDDM and IDDM ($n = 401$) ($n = 22$) | NO | YES | YES | Not stated |

N/A, not applicable

decades ago, Rundles reported that 'constipation, chronic diarrhoea, anorexia and nausea often accompany the development of diabetic neuropathy' [15]. He studied 125 patients with peripheral neuropathy selected from more than 3000 patients who were diagnosed with diabetes over a 7 year period. No information was given concerning age, gender or duration of disease. More than 60% of the patients reported gastrointestinal symptoms; 42% had constipation, this being the most frequent symptom, and 22% had chronic diarrhoea. However, it was also suggested, although not specifically quantified, that 'among an average group of diabetics receiving modern treatment, gastrointestinal disturbances' were 'probably no more frequent than among a similar group of non-diabetics'. In a follow-up study among 30 additional diabetic patients with neuropathy and gastrointestinal symptoms, abdominal pain was the most frequent symptom (in 70% of patients), followed by constipation, diarrhoea, vomiting and faecal incontinence [16].

Subsequently, a number of studies have evaluated gastrointestinal symptoms among outpatients with both type 2 (non-insulin) and type 1 (insulin-dependent) diabetes. In a sample of 136 outpatients attending a diabetes clinic, Feldman and Schiller [4] reported that 76% had one or more gastrointestinal symptoms which were, in most patients, chronic or frequently recurrent; nausea and vomiting occurred in 29%, dysphagia in 27%, abdominal pain in 34%, constipation in 60%, diarrhoea in 22% and faecal incontinence in 20% of the patients (Table 1). However, no control group was evaluated and the interview methodology applied was not well standardised, neither was the type of diabetes documented.

Clouse and Lustman [17] interviewed 114 outpatients with type 1 and type 2 diabetes; 68% reported at least one gastrointestinal symptom. Nausea was experienced by 21% of patients, abdominal pain by 32%, constipation by 12%, diarrhoea by 21% and bloating by 20%. However, no control group was evaluated.

Ko *et al*. [18] interviewed 149 patients with type 2 diabetes, using standard questions from a gastrointestinal symptom questionnaire, and 65 control subjects. They also found a high prevalence of gastrointestinal symptoms in Chinese outpatients with diabetes. Epigastric fullness was experienced by 17% of patients, abdominal pain by 16%, diarrhoea by 35% and constipation by 28% of patients; all of these symptoms were significantly more frequent than in the control group.

In contrast, Maxton and Whorwell [19] interviewed 200 patients with type 1 and type 2 diabetes attending a diabetic clinic, of whom 59 had signs of autonomic neuropathy, and 200 age- and sex-matched control subjects. They found that constipation was more common in patients with autonomic neuropathy (22% of patients) compared with patients without neuropathy (9%) and controls (7–14%). Diarrhoea was found in only 5% of patients with neuropathy and in 11% of patients without, and this was not significantly different from controls (3–6%). The prevalence of abdominal pain was also similar in patients with (19%) and without (21%) autonomic neuropathy and controls (20%).

Similarly, in 285 consecutive outpatients with type 1 and type 2 diabetes from a diabetic clinic in England, Dandona *et al*. [20] found a prevalence of 8% for diarrhoea and 5% for constipation, which was not significantly different from the prevalence in a control group of outpatients from other medical clinics. While the group of patients with diabetes who received biguanides had a higher prevalence of diarrhoea [20%], the prevalence of diarrhoea in patients who were on insulin or other oral hypoglycaemics was low (6%).

Other studies have evaluated gastrointestinal symptoms in outpatients who had type 1 diabetes. Keshavarzian and Iber [21] assessed gastrointestinal symptoms in 75 consecutive male patients with type 1 diabetes who had been on insulin for at least 5 years. Only 19% of the patients reported gastrointestinal symptoms, the most frequent being diarrhoea and constipation, with a prevalence of 5% each. Similarly, Maser *et al*. [22] evaluated gastrointestinal symptoms in a group of 168 patients with type 1 diabetes with a mean disease duration of 20.5 years; signs of autonomic neuropathy were present in 63 patients (37%). The prevalence of gastrointestinal symptoms was found to be low, with vomiting being the most frequent with a prevalence of 7%. Constipation was reported by only 3% of patients and none had diarrhoea. Enck and associates [23] evaluated 190 consecutive patients with type 1 and type 2 diabetes recruited from a diabetes research centre, and 180 age- and sex-matched controls. Symptoms arising from the upper gut were reported by 70% of patients with insulin-dependent diabetes and 44% of patients with non-insulin-dependent diabetes; 31% type 1 and 43% type 2, patients respectively, had symptoms from the lower gastrointestinal tract. However, the prevalence of gastrointestinal symptoms in diabetic patients did not differ from the prevalence in the control subjects.

In another survey using a validated questionnaire, Bytzer *et al*. [24] studied 892 randomly selected patients from a diabetes support group and 209 outpatients. To obtain information on recent glycaemic control, the authors measured glycated haemoglobin. Glycaemic control was predictive of upper, but not lower, gastrointestinal symptoms. Patients with diabetic complications had a higher frequency of most symptom groups and a higher symptom complexity.

Thus, although a number of outpatient studies have suggested that gastrointestinal symptoms are frequent, these results have not been confirmed by all investigators. Depending on the population studied, the prevalence of symptoms has varied considerably in patients with both type 1 and type 2 diabetes mellitus.

## Population-based studies of gastrointestinal symptoms in diabetes mellitus

Population-based studies of gastrointestinal symptoms in diabetic patients have been relatively few and the results conflicting (Table 1.1). To date, a total of

nine population-based studies have been undertaken evaluating gastrointestinal symptoms in subjects with diabetes mellitus [24–33]. Dyck *et al*. [24] studied 102 patients with type 1 and 278 patients with type 2 diabetes by interview. They were selected randomly from a cohort of individuals who were diagnosed with diabetes mellitus (1.3% of the total population) in the community of Rochester, Minnesota, USA ($n = 870$, 23% with type 1 and 77% with type 2 diabetes). This represents an underestimate because of the relatively high frequency of undiagnosed type 2 diabetes. Symptoms of "gastroparesis" were reported by none of the subjects with type 1 diabetes and by only 1% of subjects with type 2 diabetes. Nocturnal diarrhoea was reported by just 1% of these with type 1 diabetes and 0.5% with type 2 diabetes. The diagnostic criteria for gastroparesis and nocturnal diarrhoea were not stated and no control group was included.

Among a population of 125 subjects who were first diagnosed as having type 1 diabetes between 1960 and 1969 in the Swedish county of Örebro, Schvarcz *et al*. [25] surveyed 110 eligible subjects using a questionnaire that was previously validated for use in the general population. The prevalence of gastrointestinal symptoms was significantly higher among diabetic patients than among age- and sex-matched controls who were selected from a taxation register. In particular, anorexia (17.8% vs. 3.6%), vomiting (12.2% vs. 3.0%) and abdominal distension (42.3% vs. 24.4%) were more frequent amongst subjects with diabetes. However, the population studied was small, and only middle-aged patients who had long-standing type 1 diabetes were enrolled.

In a survey of 624 subjects with diabetes who were on a drug reimbursement register and 648 controls from the population register of Kuopio, a Finnish community, Janatuinen *et al*. [26] studied both subjects with type 1 ($n = 87$; mean age: men, 53 years; women, 56 years) and type 2 diabetes ($n = 451$; mean age: men, 56 years; women, 58 years). Subjects with type 1 diabetes had a mean disease duration of 17 years, while for those with type 2 diabetes the mean disease duration was 9 years. No differences were observed with respect to the prevalence of dysphagia, nausea, vomiting, abdominal pain, diarrhoea or constipation, and overall the prevalence of gastrointestinal symptoms was low (Figure 1.1). Frequent vomiting (once a week or more often) was experienced by 5% of patients, frequent abdominal pain ($\geq$ once a week) by 26%, constipation 'usually or always' by 16% and frequent diarrhoea ($\geq$ once a week] by 5% (Figure 1.1). However, the questionnaire used had not been validated, and patients with non-insulin-dependent diabetes mellitus who were on diet therapy only were not studied.

In another Scandinavian study, Spångéus *et al*. investigated subjects with diabetes aged 24–59 years and sex- and age-matched controls living in the Swedish county of Umeå [27]. Patients were identified by checking the registration forms

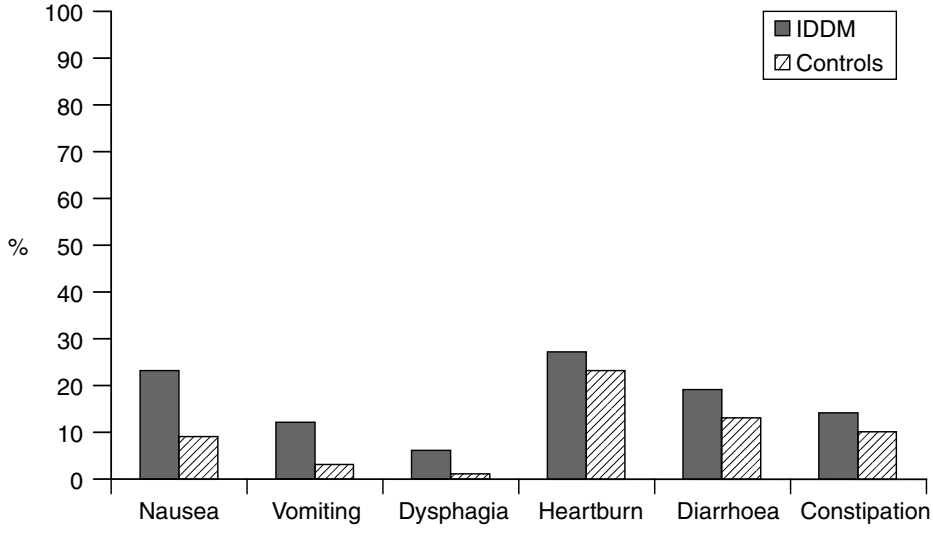


**Figure 1.1** Prevalence of gastrointestinal symptoms in 110 type 1 patients compared to controls. $^{*}p < 0.05$ type 1 vs. control. From Schvarcz *et al*. [25], with permission

of 14 primary care centres within the county. The healthy controls were medical students and hospital staff. All were mailed a validated questionnaire that was previously used by Schvarcz *et al*. [25]. The response rate among the diabetics was 59% and among the controls was 53%. Half of the patients were female and most of the responders were identified as type 1 diabetics (200 vs. 61 type 2 diabetics). The medical records of the responders were checked for glucose control, body mass index, medications and diabetes-specific complications. Patients with both type 1 and type 2 diabetes reported gastrointestinal symptoms more often than the control group. Patients with type 1 diabetes had an increased frequency of constipation (19.5% vs. 6.5% in controls); nocturnal urgency, feelings of incomplete rectal evacuation and straining were also more frequent compared to controls. In contrast, patients with type 2 diabetes had a higher frequency of abdominal pain (28.3% vs. 14.3%) and faecal incontinence (4.9% vs. 0%); they also had a higher prevalence of a nocturnal urgency, feelings of incomplete evacuation at defecation and a need to strain at defecation. Diarrhoea was not more frequent in patients with diabetes compared to controls. Patients with signs of neuropathy had a higher frequency of gastrointestinal symptoms compared to patients who had no signs of neuropathy. Other diabetic complications, such as retinopathy and nephropathy, were not associated with a higher frequency of gastrointestinal symptoms. However, the results of this study are hard to interpret, since an inadequate response rate was achieved, the patients and control subjects were not randomly selected, the proportion with type 1 diabetes was

inappropriately high and the methodology to identify diabetes complications was not standardised.

Ricci *et al*. reported on the frequency of upper gastrointestinal symptoms in a US national sample of patients with diabetes mellitus and controls who were identified by a telephone survey [28]. Of the 874 patients who identified themselves as diabetes sufferers, 483 completed a structured interview evaluating the presence of gastrointestinal symptoms within the past month. Two-thirds of the participants were women and the age range was 18–70+ years. The type of diabetes was not determined. Among the patients with diabetes, 50% reported an upper gastrointestinal symptom in the past month compared with 38% in the control group. Bloating and early satiety were more frequent in diabetics than in controls (Figure 1.4). The frequently of abdominal pain and nausea and vomiting, however, were similar in both of the groups.

A small population-based study from Olmsted County, Minnesota, evaluating the prevalence of gastrointestinal symptoms, was performed by Maleki *et al*. [29]. The authors detected no differences in the prevalence of most gastrointestinal symptoms between type 1 and type 2 diabetes and controls [30]. A slightly increased prevalence of constipation and laxative use in type 1 patients (27% vs. 19% in controls) was related to calcium channel blocker use, but not to autonomic neuropathy.

Another study was performed in Western Sydney, Australia [30]. These investigators assessed the frequency of gastrointestinal symptoms in 113 diabetics from an outpatient clinic, 400 diabetics that were selected at random from a diabetes support group, and a random sample of the general population ($n = 1000$) using a validated questionnaire; the response rates were 100%, 71% and 63%, respectively. After adjusting the results for age, sex and body mass index, none of the gastrointestinal symptoms reported was more frequent in the random diabetes population than in the control population. However, dysphagia, bloating, abdominal pain, constipation and diarrhoea were more frequent in outpatients with diabetes compared to the random diabetes population and controls. The authors also concluded that gastrointestinal symptoms may be related to glycaemic control, since the prevalence of nausea and dysphagia was greater in outpatients with glycated haemoglobin levels $\geq 10$ mg%. Other data support this conclusion [31].

In a large study from Australia, Bytzer *et al*. [32] mailed a short questionnaire containing questions on the frequency of troublesome gastrointestinal symptoms and diabetic status to a random sample of 15 000 randomly chosen adults; 60% responded. Overall, 4.9% of the responders reported diabetes (95% of whom were type 2), who were generally older than controls. The authors evaluated the frequency of five symptom complexes, i.e. oesophageal (heartburn and/or dysphagia), upper gut dysmotility, any bowel symptom, diarrhoea and constipation. After adjusting for age and gender, all symptom complexes were more

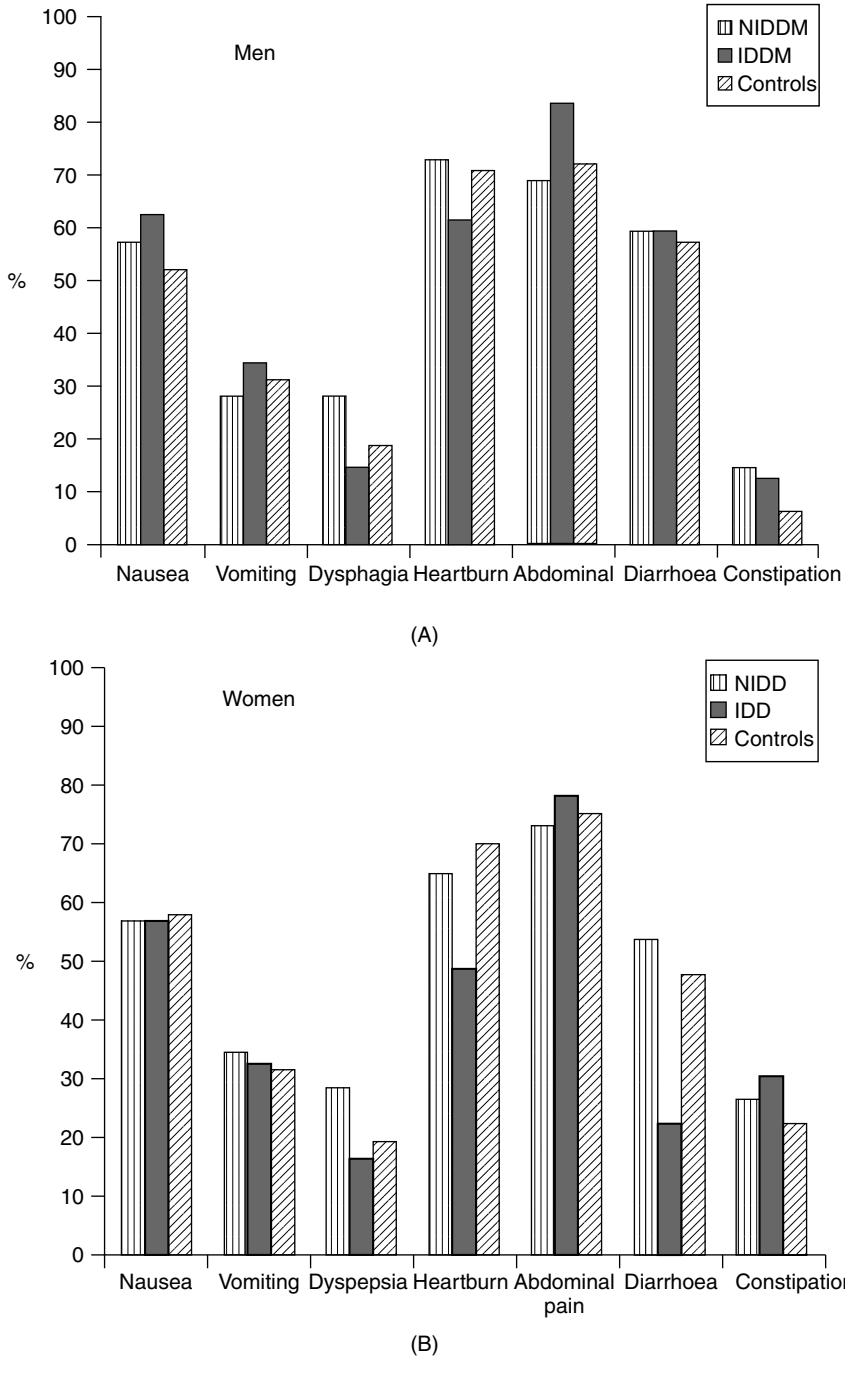


**Figure 1.2** Gastrointestinal symptoms in a population of 624 subjects with *insulin-dependent diabetes* mellitus (IDDM), *non-insulin-dependent* diabetes mellitus (NIDDM), and community controls. (a) Data in men. (b) Data in women. From Janatuinen *et al*. [26], with permission

frequent in diabetics than in controls, and the symptoms nausea, diarrhoea or constipation and faecal incontinence were independently associated with diabetes (Figure 1.2).

In conclusion, there is evidence that gastrointestinal symptoms are linked with diabetes mellitus, but the prevalence over and above the general population is at most only modestly increased. Some studies have failed to detect an association between diabetes and gastrointestinal symptoms, but several confounders may have obscured the findings. For example, it is well documented that chronic gastrointestinal symptoms are common in non-diabetics in the community, presumably due to functional gastrointestinal disorders such as the irritable bowel syndrome [33,34]. Moreover, the presence of diabetic complications and possibly long-term glycaemic control appear to be important factors in symptom onset [31,32]. This may explain the difficulty in establishing a firm link between diabetes and chronic gastrointestinal complaints in population-based studies.

## Natural history of gastrointestinal symptoms in diabetes mellitus

Community studies suggest that in the general population there is a considerable turnover of individuals reporting gastrointestinal symptoms [35,36]. Moreover, longitudinal studies in the USA [35] and Sweden [36], applying a postal questionnaire on two separate occasions, have demonstrated that the number of subjects who developed gastrointestinal symptoms in a given period of time paralleled the number of subjects who lost them [32, 35–38]. Unfortunately, almost no data exist on the natural history of gastrointestinal symptoms in diabetes, and whether factors such as glycaemic control or the development of autonomic neuropathy influence development and regression of motor dysfunction or disturbed sensation and symptoms is unknown. Indeed, it has been uncertain how many diabetic patients have gastrointestinal symptoms transiently and how many experience them for prolonged periods.

Talley *et al*. evaluated the natural history of lower gastrointestinal tract symptoms in diabetes, and assessed potential predictors of symptom change in 540 subjects with predominantly type 2 diabetes [39]. The prevalence of abdominal pain, constipation, diarrhoea and faecal incontinence was stable over a three year period, but 4–27% in these symptom groups experienced symptom turnover. Change in symptom status was not associated with change in self-rated glycaemic control or the type or duration of diabetes. Baseline complications of diabetes and psychological factors were variably associated with turnover of symptom groupings, but a consistent pattern did not emerge. Studies of the natural history of upper gastrointestinal symptoms and their relationship to glycaemic control are not available but, based on cross-sectional studies, glycaemic control may be more important in this subset [31,32].

## Potential confounders of gastrointestinal symptoms in diabetes mellitus

Here only a brief overview of factors that may alter or bias any association between gastrointestinal symptoms and diabetes will be discussed.

### Disordered motor function

In patients with long-standing type 1 and type 2 diabetes, the prevalence of delayed gastric emptying of a nutrient meal is reported to range from 27% to 40% [40–42] and the prevalence is similar in insulin-dependent and non-insulin-dependent diabetes mellitus (see Chapter 4) [43,44]. In a minority of patients (less than 10%) with long-standing diabetes, gastric emptying is accelerated [42–44]. In newly diagnosed patients with type 2 diabetes, gastric emptying of carbohydrates has been reported to be accelerated [45,46], although others have not confirmed these findings [47]. On the other hand, no data exist on the prevalence of deranged gastric emptying in patients with newly diagnosed type 1 diabetes. Manometric abnormalities were found in 81 of 84 patients with either type 1 or type 2 diabetes who completed a 3 hour fast and 2 hour postprandial motility evaluation [48]. Although some have suggested a link between gastric motor disorder and symptoms [41], most have not found a strong correlation between symptoms and either delayed [42] or accelerated gastric emptying [45]. Hence, this is a weak predictor of symptom status overall.

Delayed small bowel and colonic transit have also been reported in 20–70% of patients with long-standing diabetes mellitus (see Chapter 5) [41,49]. However, while no gastrointestinal symptoms correlated with delayed small intestinal transit, constipation (defined as less than three bowel movements/week) was significantly associated with delayed colonic transit [49].

### Autonomic neuropathy and visceral sensory dysfunction

Traditionally, gastrointestinal symptoms have been attributed to disordered motor function resulting from autonomic (vagal) neuropathy [50,51]. More recently, impaired sensory function has been implicated as a trigger for gastrointestinal symptoms in dyspeptic patients [52,53]. However, the predictive value of these abnormalities for the induction of chronic gastrointestinal symptoms is unknown.

### Glycaemic control

A number of studies have shown that acute changes in blood glucose concentrations can have a profound effect on motor function throughout the gastrointestinal

tract in both normal subjects and patients with diabetes mellitus [54]. Recent studies have demonstrated that the blood glucose concentration may also modulate the perception of sensations arising from the gastrointestinal tract [56–58]. However, there is relatively little information about the mechanisms mediating the effects of the blood glucose concentration on gastrointestinal motility. While some studies have implicated impaired glycaemic control in the genesis of chronic gastrointestinal symptoms [24,31], this remains controversial.

## Psychological factors

Psychological factors may play a role in the generation and maintenance of gastrointestinal symptoms in the general population [59]. Psychological factors are associated with both the symptoms of irritable bowel syndrome (IBS) and health care seeking by IBS sufferers [59,60]. For example, patients with IBS have higher frequencies of psychiatric diagnoses and personality disturbances, such as neuroticism, than healthy volunteers [60–62]. Further, those who see doctors for their IBS symptoms (consulters) appear to be psychologically more disturbed than those who did not seek medical attention (non-consulters) [62,63].

Psychological disorders are common in diabetics [64–70] and psychological distress and poor glycaemic control are closely associated [65,70–72]. It has thus been suggested that depression and hyperglycaemia may exacerbate one another [68]. In patients with type 1 diabetes, abnormal anxiety ratings could be identified in up to 13% and psychological abnormalities were related to age and social class, but not to duration of diabetes or glycaemic control [73]. Moreover, in elderly patients with type 2 diabetes (mean age 70 years), mental distress (defined as an elevated score in a 12-item version of the General Health Questionnaire) and depression were associated with peripheral neuropathy [74], which may reflect worse metabolic control in the group who had depression. The presence of affective and anxiety disorders has also been associated with gastrointestinal motility abnormalities in diabetic [75] and non-diabetic [76] subjects. Thus, out of 15 patients with diabetes mellitus who were found to have contraction abnormalities in the oesophageal body, such as an increased amplitude or abnormal motor response to swallowing, 13 (87%) had a psychiatric diagnosis [75].

It remains uncertain whether and to what extent psychological factors account for gastrointestinal symptoms in type 1 or type 2 diabetes mellitus, as this has not been systematically studied. Psychological distress could be the result of having a chronic illness and hence any association with symptoms could be spurious. However, Clouse and Lustman [17] found that psychiatric disturbances were more strongly related to gastrointestinal symptoms than autonomic neuropathy.

### *Helicobacter pylori* infection

*Helicobacter pylori* causes chronic histological gastritis which can progress to gastric atrophy. *H. pylori* is now established to be a cause of chronic peptic ulcer and is classified as a class 1 carcinogen by the World Health Organisation [77]. An impaired immune response in diabetes that alters both humoral [78] and cellular [79–82] immunity, and the high prevalence of upper gastrointestinal symptoms described in some studies, have led to speculation that *H. pylori* may be linked to diabetes [83]. In a recent Italian study, patients with diabetes with dyspepsia had a higher prevalence of *H. pylori* infection compared to dyspeptic controls [84]. In another study, De Luis *et al*. reported that the seroprevalence of *H. pylori* increased with increasing duration of diabetes in patients with type 1 diabetes [85]. However, others have failed to demonstrate any association between *H. pylori* and gastrointestinal symptoms in diabetes [86–88]. Moreover, no studies have adequately assessed whether cure of *H. pylori* reverses upper gastrointestinal symptoms in diabetes.

## Quality of life

### Health-related quality of life (HRQL)

HRQL refers to patients' subjective accounts of functioning and/or overall well-being in relation to health status, and encompasses emotional and physical functioning. While clinical medicine usually gauges the severity of illness and success/failure of treatment via strictly objective criteria, HRQL measures are assessed directly from patient reports. Increasingly, the concept that patient perceptions of illness and/or wellness do not necessarily correlate with objective measures of morbidity is becoming accepted [89]. Also, HRQL has critical implications, both for the individual and, when the person is unable to perform his/her daily functions, for society. Measures of function and well-being have been shown to predict both health-care expenditures and mortality [90]. Lastly, HRQL data can provide physicians with vital information on the efficacy of any given treatment regimen.

### Measurement of HRQL

Work exploring HRQL has exploded in scope and interest over the past decade (Table 1.2). Two approaches to assessing HRQL in medical illness have emerged: global and disease-specific [91]. Global HRQL measures assess daily functioning and emotional well-being without reference to specific disease symptoms (e.g. impact of illness upon communication skills). Disease-specific HRQL measures assess the impact of very specific symptoms or problems upon functioning or

**Table 1.2** HRQL studies assessing gastrointestinal symptoms

| Reference | Gastrointestinal disorder | Subjects (*n*) | HRQL instrument(s) | Gastric emptying assessed |
|---|---|---|---|---|
| Cutts *et al*., 1996 [98] | Severe dyspepsia | 27 | SIP, MMPI, MBHI | Yes, but not reported |
| Enck *et al*., 1999 [96] | Upper GI symptoms | 5581 | PGWB, IDLI | No |
| Farup *et al*., 1998 [129] | Diabetic gastroparesis | 269 | SF-36 | Yes |
| Glia and Lindberg, 1997, [107] | Functional constipation | 102 | PBWB, GSRS | Yes (Transit Time) |
| Havelund *et al*., 1999 [109] | Heartburn without esophagitus | 245 | PGWB, GSRS | No |
| Heymann-Monnikes, 2000 [132] | Irritable bowel syndrome | 24 | GQLI, Beck Depression Inventory, State–Trait Anxiety Inventory, Health and Illness-related Locus of Control Quest., Irrational Beliefs Quest. 'List of Complaints' | No |
| Drossman *et al*., 2000 [102] | Functional bowel disorders | 156 | SIP, IBS–QOL | No |
| Drossman *et al*., 2000 [134] | Functional bowel disorders | 211 | SIP, IBS–QOL, SCL-90 Beck Depression Inventory, five others | No |
| Koloski *et al*., 2000 [95] | Functional bowel disorders | 2910 | SF-12, Eysenck Personality Quest Sphere, Delusions–Symptoms–States Inventory (DSSI) | No |
| Mathias *et al*., 1998 [115] | Functional bowel disease | 100 | SF-36, Visual Analogue Scale | No |
| O'Keefe *et al*., 1995 [117] | Functional bowel disorders | 533 | SF-36 | No |
| Revicki *et al*., 1998 [108] | gastrooesophageal reflux disease | 533 | SF-36 | No |
| Revicki *et al*., 1999 [110] | gastrooesophageal reflux disease | 1351 | SF-36, PGWB | No |
| Rockwood *et al*., 2000 [105] | Faecal incontinence | 190 | Faecal Incontinence QOL Scale SF-36 | No |
| Sailer *et al*., 1998 [118] | Faecal incontinence | 209 | GQLI | No |
| Sailer *et al*., 1998 [119] | Benign anorectal disorders | 325 | GQLI | No |
| Silvers *et al*., 1998 [112] | Diabetic gastroparesis | 269 | SF-36 | Yes |
| Soykan *et al*., 1997 [113] | Gastroparesis | 17 | SF-36 | Yes |
| Soykan *et al*., 1998 [111] | Gastroparesis | 146 | MBHI, SCL-90, CES-D Depression Scale, Visual Analogue Scale | Yes |
| Snijders *et al*., 1998 [116] | AIDS | 62 | Diary Cards, Interview | No |

**Table 1.2** (*continued*)

| Reference | Gastrointestinal disorder | Subjects (*n*) | HRQL instrument(s) | Gastric emptying assessed |
|---|---|---|---|---|
| Talley *et al*., 1999 [106] | Functional dyspepsia | 101 | Nepean Dyspepsia Index, SF-36, Beck Depression Inventory, State–Trait Inventory, Bowel Symptom Questionnaire Global Assessment | No |
| Wiklund *et al*., 1998 [103] | gastrooesophageal reflux disease, dyspepsia | | Quality of Life in Reflux and Dyspepsia, GSRS, SF-36 | No |
| Wong *et al*., 1998 [101] | Irritable bowel syndrome | 12 | IBS Questionnaire | No |
| Sailer *et al*., 1998 [119] | Benign anorectal disorders | 325 | GQLI | No |

GQLI, Gastrointestinal Quality of Life Index; GSRS, Gastrointestinal Symptom Rating Scale; IBS–QOL, Irritable Bowel Syndrome Quality of Life assessment; IDLI, Interference with Daily Life Index; MBHI, Millon Behavioral Health Inventory; MMPI, Minnesota Multiphasic Personality Inventory; PGWB, Psychological General Well-being Index; SF, short form; SIP, Sickness Impact Profile; QOL, quality of life; Quest., questionnaire; GI, gastrointestinal.

well-being, e.g. level of social embarrassment due to having a colostomy. No gold standard exists in terms of assessing HRQL in gastrointestinal disease and researchers disagree on the best approach [92].

In terms of type of HRQL instruments and diabetes, Jacobson and colleagues compared global vs. disease-specific measures in patients with type 2 diabetes [93]. These researchers concluded that, when examining the impact of acute complications and/or regimens on HRQL, a disease-specific measure was most appropriate. A global measure (Medical Outcomes Study Short Form or MOS SF-36) was deemed most useful for examining relationships between patients' experience of living with diabetes and other chronic diseases. Likewise, Anderson *et al*. [94] found that, in a sample of 255 type 2 diabetic patients, exploring 'within-disease' parameters was best assessed via a disease-specific instrument, while relationships 'between' patient experiences of living with diabetes and HRQL and other diseases were best captured via global measures. Several studies examining the impact of HRQL upon patients with upper gastrointestinal distress (typically dyspepsia) have utilised global measures, usually the SF-36 or some variant of that scale [89,95]. Similarly, a larger-scale study [96] investigated HRQL in patients with upper gastrointestinal symptoms from seven European countries, USA, Canada and Japan. This work concluded that, of the 5581 respondents (27% of whom also were diagnosed with diabetes, hypertension or asthma), the presence of gastrointestinal symptoms was associated with impaired well-being and daily life, as measured via the Psychological General Well-being Index (PGWB) and Interference with Daily Life Index (IDLI). Subjects with upper gastrointestinal symptoms (particularly ulcer-like symptoms) manifested poorer scores on these HRQL measures.

Others have opted to use batteries of assessment, encompassing both global and disease-specific measures [97,98]. For example, Talley *et al*. [97] applied a battery of validated measures, which included a short form of the Medical Outcomes Survey (SF-12), a Brief Symptom Inventory and gastrointestinal symptoms. The authors found that patients with functional dyspepsia had poorer mental health, social functioning and health perception, compared with patients with other conditions who presented for upper endoscopy.

Disease-specific measures in gastrointestinal diseases have been developed for several disease entities, including inflammatory bowel disease [99], IBS [100–102], gastro-oesophageal reflux disease (GORD) [103,104], faecal incontinence [105] and functional dyspepsia [106], with varying degrees of psychometric validation. However, no disease-specific quality of life measure exists for gastrointestinal dysfunction in diabetes.

## Specific gastrointestinal symptoms and HRQL

Several gastrointestinal symptoms have been specifically related to a deranged HRQL (Table 1.2). Patients with constipation have lower general HRQL scores than healthy controls [107], as have patients with heartburn [108–110]. Appropriate treatment of gastro-oesophageal reflux disease decreased heartburn and in turn increased HRQL scores [108–110]. Nausea and vomiting in patients with severe dyspepsia or gastroparesis was also associated with a decrease in HRQL [98,111]. Patients who were successfully treated for their symptoms showed a significant enhancement of HRQL [98,111–113]. The severity of abdominal pain in patients with functional bowel disease correlates with impaired HRQL and increased levels of psychological distress [114]. When abdominal pain scores improved after treatment, so also did HRQL, as evaluated by the use of the SF-36 [115]. There was also a significant correlation between the change in scores on the IBS–QOL, a disease-specific quality of life scale for patients with IBS, and average daily pain level over two 14 day periods [101]. The IBS–QOL scores discriminated responders to treatment from non-responders for the pain level parameter. Finally, even mild diarrhoea (assessed via diary cards and interview) was perceived as having a debilitating effect on HRQL (assessed via interview) in patients infected with HIV [116]. In a random sample of elderly patients, role functioning scale scores discriminated patients with diarrhoea from asymptomatic controls [117].

The impact of faecal incontinence, an important complication of diabetes (see Chapter 6), on HRQL was investigated by Sailor *et al*. [118,119], using the Gastrointestinal Quality of Life Index [GIQLI]. They evaluated HRQL in patients with faecal incontinence, compared with those with haemorrhoids or fissure in ano, and healthy controls. Patients with faecal incontinence manifested the lowest HRQL scores, compared to both medical and healthy control groups [117]. Subgroups of patients with faecal incontinence and severe constipation had the poorest HRQL scores [119].

## Diabetes and HRQL

As part of the Medical Outcomes Study, that determined the impact of nine different chronic illnesses upon HRQL, Stewart *et al*. [90] used the Short Form (SF-20) of the General Health Survey to evaluate HRQL ratings in 9385 patients, 844 of whom had diabetes (92% were type 2 diabetics and 44% had one or more physician-reported complications). Diabetic patients in this study reported lower HRQL scores than control patients with other chronic conditions. Also, after controlling for sex, age, income and education, subjects with diabetes reported significantly lower scores on all summary scales (physical, role, social functioning, health perceptions) except for mental health. Moreover, gastrointestinal disorders had a more negative impact on HRQL than all other conditions with the exception of heart disease [90]. Others have reported similar findings [120,121].

Jacobson *et al*. [93] assessed HRQL in 240 diabetic patients (54% were type 2 diabetics) and controlled for age, marital status, education, illness duration and severity of complications. Compared with patients with type 1 diabetes, patients with type 2 diabetes reported less of an impact of diabetes and fewer worries about their illness on the diabetes-specific quality-of-life scale, the DQOL, used in the Diabetes Control and Complications Trial (DCCT), as well as better social functioning on the SF-36.

## Gastrointestinal complications of diabetes and HRQL

A study of diabetic patients undergoing transplantation [122] indicated that, of all the factors likely to compromise HRQL, the single most important one was gastrointestinal dysfunction. Drenth and Engel suggested that symptoms of nausea, vomiting, bloating/distension, early satiety and abdominal pain likely all play a role in this perception [123]. Talley *et al*. evaluated quality of life using the SF-36 and gastrointestinal symptoms in 209 outpatients and 892 community subjects with diabetes; quality of life scores were decreased in diabetics with gastrointestinal symptoms, and decreased markedly with increased numbers of gastrointestinal symptoms [124] (Figure 1.4). Moreover, gastrointestinal symptoms were significantly associated with poorer quality of life after adjusting for age, gender, smoking, alcohol use and type of diabetes [124]. Siddique *et al*. evaluated upper gastrointestinal symptoms and quality of life using the SF-12 in 483 community subjects with self-reported diabetes and 422 age- and gender-matched controls in the USA [125]. They observed that upper gastrointestinal symptoms were associated with more impaired physical and mental health summary scores; on the other hand, individuals with diabetes and no gastrointestinal symptoms had quality of life scores similar to healthy subjects. Early satiety and nausea were the strongest predictors of physical and mental health score differences, respectively, in those with and without diabetes.

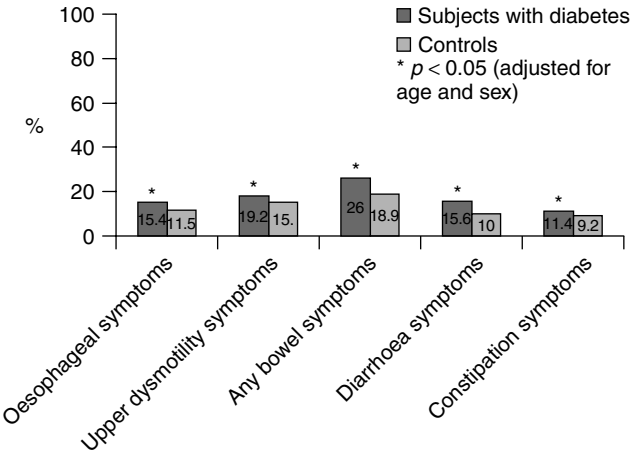


**Figure 1.3** Prevalence of gastrointestinal symptom complexes in a population-based study: predominantly type 2 diabetes ($n = 423$) and controls ($n = 8185$). From Bytzer *et al*. [31], with permission

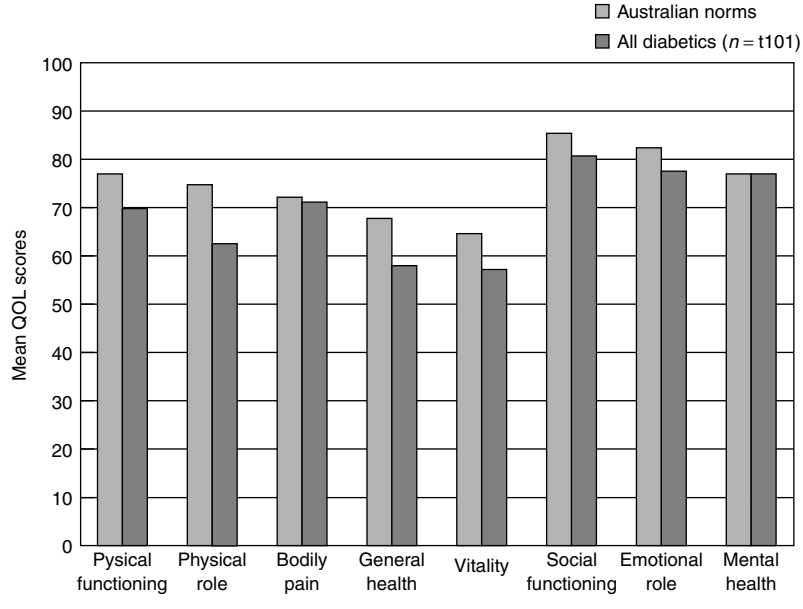


**Figure 1.4** A comparison of quality of life scores across SF-36 subscales in subjects with diabetes and normal Australian population data. From Talley *et al*. [124], with permission

## Glycaemic control and changes in HRQL

Testa and Simonson [126], attempting to overcome the uncontrolled nature of earlier studies, conducted a randomised, controlled, double-blind study of the

short-term impact of glycaemic control upon HRQL in patients with type 2 diabetes. They concluded that treatment, and subsequent good glycaemic controls was associated with improved HRQL (measured using a visual analogue scale) and a number of health economic indices related to work (e.g. less absenteeism, greater work productivity, fewer bed days and fewer restricted activity days). Additionally, these researchers concluded that the rate of HRQL deterioration due to increasing symptoms was progressive with worsening glycaemic control, suggesting, on the other hand, that improvement of glycaemic control also might facilitate the improvement of the HRQL.

## Prokinetic therapy in diabetes and quality of life

Studies assessing prokinetic therapy for gastrointestinal symptoms and HRQL in both diabetic patients and those with alternative aetiologies have proliferated over the last decade [97,110,111,127]. A number of these studies have assessed HRQL in addition to traditional symptom improvement indices. Cutts *et al*. [98] found that one year of treatment with prokinetic therapy (cisapride or domperidone) resulted in improved HRQL as measured by the Sickness Impact Profile (SIP), as well as symptom improvement in a group of patients with severe dyspeptic symptoms of both diabetic and idiopathic aetiologies. Soykan *et al*. [111] followed 146 patients with 'gastroparesis' symptoms and delayed gastric emptying, treated with prokinetic therapy and other treatment modalities for six years after initial diagnosis. They assessed psychological and HRQL (by visual analogue scale) parameters, as well as gastric emptying and gastrointestinal symptoms, and found that 74% responded favourably to prokinetic therapy. Also, those patients with a presumed viral aetiology had greater symptom resolution and improved HRQL, as compared to their idiopathic counterparts. The same group of researchers investigated the use of oral domperidone in the treatment of 17 patients with a documented delay in gastric emptying [113]. They found that domperidone therapy (average 23.3 months) significantly reduced nausea, vomiting, abdominal pain and bloating and resulted in enhanced HRQL (measured via select questions from the SF-36) in 88% of the patients treated, with minimal side effects (three patients developed gynaecomastia). Of the 15 patients re-evaluated at follow-up, gastric emptying of a solid meal was significantly accelerated to a normal rate. However, none of the studies cited above compared their samples to matched controls, and Cutts *et al*. did not document delayed gastric emptying (Table 1.2).

Rashed *et al*. [128] examined autonomic functioning as a determinant of quality of life improvement in a group of seven patients with diabetic gastroparesis, in an uncontrolled study. These investigators compared patients in an open label trial of domperidone for 12 months, assessing gastrointestinal symptoms via the Total Symptom Score (TSS), a summed index gathered from patient reports, HRQL via the SIP and autonomic functioning, reported as the total autonomic

score (TAS), previously described [129]. Patients showed a significant improvement of 56% in the total symptom score at baseline vs. 12 months. SIP scores improved in six of seven patients, with a median improvement level of 22%, from baseline to one year. Autonomic functioning status at baseline correlated significantly with the SIP Psychosocial Dimension scale (measuring emotional behaviour, communication, social interaction, and alertness behaviour). Hence, in the small sample of diabetic gastroparesis patients, domperidone use was associated with improvement in both gastrointestinal symptoms and HRQL. However, in patients with impaired autonomic functioning, the level of HRQL manifested less improvement. These findings may have implications for selection of diabetic patient subgroups that may benefit from prokinetic therapy.

These data were substantiated in the recent multi-centre examination of the effect of treatment with domperidone on HRQOL in diabetic gastropathy [112,130]. Silvers *et al*. [112] and Farup *et al*. [130] reported on use of domperidone therapy in a sample of patients with insulin-treated diabetes and symptoms of gastroparesis. These researchers conducted a four-week, double-blind, placebo-controlled study and found that patients who responded favourably to domperidone experienced significantly improved gastrointestinal symptom relief and HRQL (measured via the SF-36) compared to placebo. In a long-term follow-up of idiopathic gastroparesis, 12 patients (all of whom had taken prokinetic drugs at some point) of presumed viral aetiology reported improved HRQL (measured via the SF-20), compared to the remainder with gastroparesis [127]. These results suggest that prokinetic therapy is useful in the treatment of gastrointestinal symptoms in both diabetic and idiopathic subgroups of patients. Domperidone therapy may potentially be most efficacious in those diabetic patients with delayed gastric emptying who have preserved autonomic function [131].

In addition to prokinetic therapies and HRQL, gastric electrical stimulation is currently being investigated in multi-centre trials across the USA and internationally [132,133]. Preliminary results indicate that, over a 24 month treatment of 28 patients with severe dyspepsia (primary symptoms of intractable nausea and vomiting), gastric pacing was associated with significant changes in sympathetic cholinergic function, decreased gastrointestinal symptoms and HRQL [134]. Recent approval of this treatment modality of gastric pacing as a Humanitarian Use Device by the US Food and Drug Administration will allow further exploration of this treatment for patients who do not respond to, or cannot tolerate, available drug therapies.

In conclusion, measurement of health-related quality of life provides the physician with another tool with which to monitor a patient's progress during long-term treatment for chronic disease, such as diabetes mellitus. This type of assessment also provides a vehicle for communication between physician and patient—a means for the physician to understand the phenomenological

'experience' of the disease and promote treatment. In diabetic patients with gastrointestinal symptoms, which can further complicate self-management and so easily lead to discouragement and frustration, this may prove to be one of the most valuable applications of HRQL information.

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