

Poor glycaemic control is the major factor associated with increased frequency of gastrointestinal symptoms in patients with diabetes mellitus

Shahab Abid¹, Amir Rizvi¹, Firdous Jahan², Fauziah Rabbani³, Najmul Islam¹, Masood H. Khan⁴, Rana Masood⁴, Wasim Jafri¹

Departments of Medicine¹, Family Medicine² and Community Health Sciences, Aga Khan University, and Department of Medicine, Civil Hospital, Karachi³, Pakistan.

Abstract

Objective: To compare the GI symptoms in diabetic patients with controls and its relationship with the complications, duration of diabetes and glycaemic control.

Methods: Consecutive patients were prospectively enrolled in to two groups. Group I (diabetic patients) and Group II (non-diabetic, Controls). Patient's characteristics, demographic profiles and GI symptoms were evaluated on a questionnaire. Groups were compared for differences in various GI symptoms. Group I was further analyzed for the relationship between GI symptoms with complications, duration of diabetes and glycaemic control.

Results: A total of 514 patients were enrolled 250 were diabetics (group I) and 264 were non-diabetics (group II). Mean age was 51.8 ± 10.6 years and 50.2 ± 9.2 years in groups i and ii respectively. All GI symptoms; heartburn, dyspepsia, bowel related abdominal pain, diarrhea, constipation, and faecal incontinence were significantly more in diabetics than controls ($P < .05$).

The presence of diabetic neuropathy, retinopathy and HbA1c of >7 were significantly ($P < .05$) related to GI symptoms. Duration of diabetes (>10 years) was not found significantly linked to GI symptoms.

Conclusions: GI symptoms in diabetics were more frequent then control subjects and were significantly associated with poor glycaemic control, neuropathy and retinopathy but not with duration of diabetes. Number of GI symptoms increases with the severity of poor glycaemic control in diabetic patients (JPMA 57:345:2007).

Introduction

GI symptoms are common in the general population, particularly the symptoms of dyspepsia.¹ Studies have shown that GI symptoms are more frequent in diabetic patients compared to non-diabetic controls but results are still diverging.² For instance, by using self administered, mailed questionnaires, results obtained showed no differences in the prevalence of GI symptoms when diabetic patients were compared with controls.³ On the other hand in a population based survey it was found that diabetes mellitus is associated with an increased prevalence of upper and lower GI symptoms.⁴ Moreover the link between duration of diabetes and development of GI symptoms were found to be confusing. A study done in the Chinese population showed significant link between the duration of diabetes and the frequency of GI symptoms⁵, while in another study, duration of diabetes or type of treatment was not found to be associated significantly with increased frequency of GI symptoms in diabetics.⁴ Similarly the pathogenesis of GI symptoms in diabetic patients remains poorly defined. It has been suggested that symptoms reflect abnormal GI motility as a manifestation of irreversible autonomic neuropathy.⁶ However other factors are also

important e.g. acute changes in blood glucose, poor glycemic control and fluctuation in insulin level⁷ and associated infections notably *Helicobacter pylori*.⁸

The aim of this study was therefore to examine the prevalence of GI symptoms in type II diabetic patients treated at a diabetes clinic compared to control subjects. In addition, the relationship between the duration of diabetes, glycaemic control and complications of diabetes with the prevalence of GI symptoms in diabetic patients was also determined.

Patients and Methods

This prospective study was performed at out patient's clinic of two major hospitals (Aga Khan University Hospital, a private university hospital and Civil Hospital - Karachi, a major hospital in public sector) from September 2002 to November 2003. The diabetes clinics of these hospitals cater to out-patients who seek care for their diabetes control and for the management of diabetes related complications. The patients in both hospitals are from diverse socio-economic and ethnic backgrounds and hence represent the general diabetic population at large.

Study subjects were divided into two groups. Group

I (diabetic patients) attending diabetes clinic and Group II (non-diabetic, controls) who were randomly enrolled from executive check-up clinic or pre-employment medical examination and those who were attending medical outpatients clinics for some other reason. The following patients were excluded: (i) those with previous history or newly documented organic GI lesion, including peptic ulcer (diagnosed on endoscopy), biliary stones or other pathology in biliary system, GI tract tumor, prior GI surgery, scleroderma or other connective tissue diseases, anatomical obstruction or stricture; (ii) those with impairment of hepatic or renal function; (iii) those with other medical disorders, e.g. heart failure, cerebro-vascular accident; (iv) Type 1 diabetic patients, defined by an acute presentation with ketoacidosis or heavy ketonuria (>3+) or starting insulin within 1 year of diagnosis, and requiring insulin continuously thereafter.⁹ All patients were evaluated by a questionnaire¹⁰ which contained detailed information about upper and lower abdominal symptoms within the last 12 months. All symptoms that are not completely self-explanatory were anchored to a standard description. The following eight GI symptoms groups were used for screening. Unless stated otherwise, a symptom was counted only if reported to occur more than 25% of the time over the past 12 months. The questionnaire was filled by the patients themselves with the assistance of non-medical staff blinded for the diabetes status of the patient.

1. Gastroesophageal reflux symptoms-heartburn or acid regurgitation at least once a week.
2. Dysmotility like Dyspepsia-epigastric pain or discomfort in combination with any upper dysmotility symptom (early satiety, postprandial fullness, bloating, abdominal swelling, nausea [at least two to three times a month], vomiting [at least once a month], and retching [at least once a month]).
3. Ulcer like dyspepsia-localized epigastric pain or discomfort combined with at least two of the following characteristics: night pain, episodic pain, pain relieved by antacids, pain relieved by food or milk, pain provoked by being hungry.
4. Bowel-related abdominal pain, abdominal pain or discomfort associated with at least two of three features (relieved with defecation, onset associated with a change in the frequency of stool, onset associated with a change in stool form).
5. Diarrhoea-very loose or watery stools more than 75% of the time and no abdominal pain.
6. Constipation-at least two of the following symptoms: <3-bowel movements/week, anal blockage, manual dis-impaction, lumpy or hard stools, incomplete evacuation, straining or patient taking fibers such as bran, cereal or ispagulla husk daily to relive

constipation.

7. Frequent abdominal pain-abdominal pain of at least moderate intensity occurring minimally once a week over the past 12 months.
8. Faecal incontinence-leakage of bowel movements about once a month or more frequently.

The diabetic complications were classified as present according to the following definitions:

- * Nephropathy: the patient answered yes to the question "Did your doctor tell you about any kidney damage or protein in your urine that is a result of your diabetes?"
- * Peripheral neuropathy: the patient answered yes to the question "Do you suffer from 'pins and needles' in your feet or hands?"
- * Retinopathy: the patient answered yes to the question "Are you aware of any eye damage that is a result of your diabetes?" and had received laser therapy.

Demographic profile, biochemical parameters, duration of diabetes and HbA1c levels (last level available at the time of filling the questionnaire), were also recorded.

Statistical analysis was performed using SPSS (version 11.5; SPSS, Chicago, IL). All results are expressed as mean + SD. The analysis of covariance and chi-square test were used for between group comparisons where appropriate. Multivariate analysis was used to examine the independent relationship between scoring for GI symptoms and the following: duration of diabetes, presence of various complications and HbA1c. A P-value <0.05 was considered to be significant.

Institutional ethical committee's approval was obtained from both study centers prior to the start of the study. Informed consent was obtained from the patients before filling the questionnaire.

Results

A total of 514 consecutive patients were enrolled Group I (diabetic patients) had 250 (48.64%) and Group II (non-diabetics- control) 264 (51.36%). Patients with diabetes (Group I) were slightly older (mean age 51.8± 10.6 years) compared to non-diabetic patients (Group II, mean age of 50.2 ± 9.2 years). Both groups had predominance of females. All eight-symptom groups were reported more frequently in Group I compared to group II, p< 0.05 (Table 1).

A large proportion (44%) of patients had diabetes more than 10 years and their mean HbA1c was 7.8%. Neuropathy was present in 130 (52%); retinopathy in 102 (40.8%) and nephropathy in 14 (5.6%) patients with diabetes.

Complications of diabetes such as peripheral

Table 1. Patient's characteristics and Comparison of Gastrointestinal symptoms between Group I (diabetics) and Group II (controls).

Patients characteristics and Gastrointestinal Symptoms	Group I (Diabetics)	Group II (Controls)	P value
	N=250 (%)	N=264 (%)	
Age (mean ± SD)	51.8 yrs ± 10.6	50.2 yrs ± 9.2	
Females (%)	56	59.8	
Smokers (%)	8	10	
Alcohol users (%)	3	5	
Gastroesophageal reflux symptoms	110 (44)	57 (21.6)	.001
Dysmotility like dyspepsia	88 (35)	27 (10.2)	< .001
Ulcer like Dyspepsia	40 (16)	18 (6.8)	.05
Bowel related abdominal pain	38 (15.2)	6 (2.2)	.001
Diarrhea	32 (12.8)	6 (2.2)	.007
Constipation	114 (45.8)	42 (15.9)	< .001
Frequent abdominal pain	32 (12.8)	12 (4.5)	.03
Fecal Incontinence	22 (8.8)	0	< .001

Table 2: Relationship between duration and complications of diabetes mellitus with Gastrointestinal symptoms.

Group I (Diabetic patients)	GI symptoms (1 or >)		P value
	Present	Absent	
Diabetic Nephropathy n=14	8	6	NS*
Diabetic Neuropathy n=130	106	24	.045
Diabetic Retinopathy n=102	86	16	.035
HbA1c < 7 n=74	44	30	NS*
HbA1c ≥ 7 n=176	142	34	.015
Duration of Diabetes < 10 yrs n=140	102	38	NS*
Duration of Diabetes >10 yrs n=110	84	26	NS*

*NS = Non-significant. P > 0.5

Table 3. Relationship between Number of Gastrointestinal symptoms Reported and Glycated Hb (n=250).

Symptoms	Patients (%)	Mean HbA1c
0 symptom	64 (25.6)	7.3
1 symptom	54 (21.6)	7.5
2 symptoms	54 (21.6)	8.5
3 symptoms	30 (12)	7.9
4 symptoms	28 (11.2)	8.4
5 symptoms	10 (4)	8.6
6 symptoms	10 (4)	8
7 symptoms	0 (0)	-

neuropathy and retinopathy were significantly associated ($p < 0.05$) with occurrence of one or more GI symptoms, whereas nephropathy was not found to be associated with increase frequency of GI symptoms among diabetic patients. GI symptoms were present more frequently in diabetic patients with HbA1c level of >7 ($p=0.015$). However, duration of diabetes mellitus (more than 10 years)

was not found significantly associated with increased frequency of GI symptoms. The relationship between duration of diabetes and its complications with the presence of GI symptoms are shown in Table 2.

Almost 75 percent of diabetic patients reported at least one or more GI symptoms. All eight GI symptom-groups were reported more frequently when the HbA1c level was 7 or more. The frequency of gastro esophageal reflux and dyspepsia was higher. More than half of diabetic patients (52.8%) had two or more symptoms with HbA1c level of > 7.9 . The number of GI symptoms reported by 250 diabetic patients and the relationship with HbA1c level is summarized in Table 3.

Discussion

It has been found that GI symptoms in diabetics are associated with significant impact on the quality of life. In one study¹¹ up to 76% of patients attending diabetes clinic had GI symptoms when specifically questioned. This study also shows that all eight GI symptom groups were more prevalent in diabetic individuals than controls. It was also observed that the number of symptoms group increased with the severity of poor glycaemic control in type II diabetes.

Several studies have shown that acute changes in blood glucose concentration have a major effect on motor function throughout the GI tract in healthy subjects and in patients with diabetes.^{12,13} Variations in blood glucose concentration also have the potential to affect symptoms arising from the GI tract.¹⁴ Studies have shown that the perception of nausea, occurring as a result of proximal gastric distention, is greater during hyperglycaemia.⁴ Acute hyperglycaemia was found to be associated with delayed gastric emptying in diabetics.¹⁵ It reduces lower esophageal sphincter pressure and velocity of esophageal peristalsis and alters motility of small intestine and gall bladder.¹⁶ Recently it has been demonstrated that hyperglycaemia can trigger transient lower esophageal relaxation and contribute to the increased esophageal acid exposure in patients with diabetes mellitus.⁷ Controversy still exists as some studies showed a direct relationship between glycaemic control and GI symptoms^{4,17} while others differ.⁵

Based on our observations, we believe that acute or sub-acute changes in glucose concentration (as reflected by HbA1c levels) are a key factor associated with increased frequency of GI symptoms. In our study it has been observed that the upper GI symptoms were significantly more in patients with glycated HbA1c of 7 or more. This might be due to the direct effect of hyperglycaemia over the vagus nerve, causing delayed gastric emptying, increased degree of relaxation of proximal stomach or a central action

of hyperglycaemia over the brain vagal nuclei. These possible mechanisms suggest hyperglycaemia associated significant increase in upper GI symptoms in diabetics.⁷

There are several other factors, which may be responsible for increased GI symptoms in diabetics such as autonomic neuropathy and concurrent infections. Despite its significant negative impact on survival and quality of life, diabetic autonomic neuropathy is among the least recognized and understood complication of diabetes. Several hypotheses concerning the multiple etiologies of diabetic neuropathy include a metabolic insult to nerve fibres, neurovascular insufficiency, autoimmune damage and neuro-hormonal growth factor deficiency. Hyperglycaemic activation of the polyol pathway leading to accumulation of sorbitol and potential changes in the NAD: NADH ratio may also cause direct neuronal damage. GI manifestations of autonomic neuropathy are diverse and symptoms and pathogenic mechanisms have been categorized according to the specific part of the affected GI tract. Esophageal dysfunction results at least in part from vagal neuropathy. Delayed gastric emptying largely depends on vagus nerve function, which can be severely disrupted in diabetes. Autoantibodies to autonomic nerves have been demonstrated, associated with the development of autonomic neuropathy in type 1 diabetics.¹⁸ Diarrhoea, which is typically intermittent and faecal incontinence due to poor sphincter tone, may be related to autonomic neuropathy. The present study has shown a significant association between diabetic neuropathy and retinopathy and GI symptoms in diabetics.

Despite significant association of increase frequency of GI symptoms in diabetics with neuropathy in our study, we cannot conclude that neuropathy alone was responsible for GI symptoms. This is because of the fact that no association was found between duration of diabetes (that usually correlates with the development of neuropathy) and GI symptoms in our study. A large population based survey concluded that neither poor glycaemic control nor autonomic neuropathy alone is enough to explain the pathogenesis of GI symptoms in all diabetic patients.⁴ However as evident from our study, poor glycaemic control plays an important role in generation of at least upper GI symptoms in diabetics.

Certain GI infections may also play an important role in causation of GI symptoms; at least in a subset of diabetic patients. It might be interesting to note that a high prevalence of *Helicobacter pylori* was found among diabetics compared to controls in a recently published study associated with dyspeptic symptoms.⁸ Moreover concurrent use of certain drugs may be important in causing GI symptoms in diabetics. However a study has recently

reported that troublesome GI symptoms in patients with diabetes do not appear to be caused by use of oral hypoglycaemic medications or other drugs, except for diarrhea which is strongly and independently associated with metformin use.¹⁹

In summary, this study has provided further evidence that both upper and lower GI symptoms were significantly more common in type II diabetic patients compared to controls. Poorer glycaemic control was associated with significant increase in upper GI symptoms. Moreover long-term complications such as neuropathy and retinopathy were found to be associated with increased frequency of GI symptoms. However the duration of diabetes was not found to be associated with increase in the frequency of GI symptom in our study.

It is therefore important that Gastroenterologists start seeking support from other disciplines such as dieticians, public health physicians and family medicine practitioners. Attention should be directed towards health promotion (e.g. smoking cessation and weight reduction) and secondary diabetes prevention methods in order to better manage diabetes and thus bring down case load related to GI symptoms amongst diabetic patients.

References

1. Agreus L, Svardsudd K, Nyren O, Tibblin G. Irritable bowel syndrome and dyspepsia in the general population: overlap and lack of stability overtime. *Gastroenterology* 1995; 109:671-80.
2. Lluich I, Ascaso JF, Mora F, Minguez M, Pena A, Hernandez A et al. Gastroesophageal reflux in diabetes mellitus. *Am J gastroenterol* 1999; 94:919-24.
3. Maleki D, Locke GR, Camilleri M, Zinsmeister AR, Yawn BP, Leibson C et al. Gastrointestinal tract symptoms among persons with diabetes mellitus in the community. *Arch Intern Med* 2000; 160:2808-16.
4. Bytzer P, Talley NJ, Leemon M, Young LJ, Jones MP, Horowitz M. Prevalence of Gastrointestinal symptoms associated with diabetes mellitus. A population based survey of 15,000 adults. *Arch Intern Med* 2001; 161:1989-96.
5. Ko GT, Chan WB, Chan JC, Tsang LW, Cockram CS. Gastrointestinal symptoms in Chinese patients with type-2 diabetes mellitus. *Diabet Med* 1999; 16:670-4.
6. Enck P, Rathmann W, Spiekermann M, Czerner D, Tschope D, Zeigler D et al. Prevalence of gastrointestinal symptoms in diabetic patients and non-diabetic subjects. *Z Gastroenterol* 1994; 32:637-41.
7. Zhang Q, Horowitz M, Rigda R, Rayner C, Worynski A, Holloway RH. Effect of hyperglycemia on triggering of transient lower esophageal sphincter relaxations. *Am J Physiol Gastrointest Liver Physiol* 2004; 286:797-803.
8. Gulcelik NE, Kaya E, Demirbas B, Culha C, Koc G, Ozkaya M, et al. *Helicobacter pylori* prevalence in diabetic patients and its relationship with dyspepsia and autonomic neuropathy. *J Endocrinol Invest.* 2005; 28:214-7.
9. Laakso M, Pyorala K. Age of onset and type of diabetes. *Diabetes Care* 1985; 8:114-7.
10. Talley NJ, Phillips SF, Melton J, Wiltgen C, Zinsmeister AR. A patient questionnaire to identify bowel disease. *Ann Intern Med.* 1989; 111:671-4
11. Feldman M, Schiller LR. Disorders of gastrointestinal motility associated with diabetes mellitus. *Ann Intern Med* 1983; 98:378-84.
12. Rayner CK, Smout AJ, Sun WM, Russo A, Semmler J, Sattawatthamrong Y et al. Effects of hyperglycemia on cortical response to esophageal distension in normal subjects. *Dig Dis Sci.* 1999; 44:279-85.
13. Samsom M, Akkermans LM, Jebbink RJ, Van Isselt H, Van Berge-

- Henegouwen GP, Smout AJ. Gastrointestinal motor mechanism in hyperglycemia induced delayed gastric emptying in type I diabetes mellitus. *Gut* 1997; 40:641-6.
14. Jones KL, Horowitz M, Berry M, Wishart JM, Guha S. Blood glucose concentration influences postprandial fullness in IDDM. *Diabetes Care* 1997; 20:1141-6.
 15. Horowitz M, Harding PE, Maddox AF, Wishart JM, Akkermans LM, Chatterton BE et al. Gastric and esophageal emptying in patients with type-2 (non-insulin dependent) diabetes mellitus. *Diabetologia* 1989; 32:151-9.
 16. de Boer SY, Masclee AA, Lam WF, Lamers CB. Effect of acute hyperglycemia on esophageal motility and lower esophageal sphincter pressure in humans. *Gastroenterology* 1992; 103:775-80.
 17. Bytzer P, Talley NJ, Hammer J, Young LJ, Jones MP, Horowitz M. GI symptoms in diabetes mellitus are associated with both poor glycemic control and diabetic complications. *Am J Gastroenterol* 2002; 97:604-11
 18. Granberg V, Ejksjaer N, Peakman M, Sundkvist G. Autoantibodies to autonomic nerves associated with cardiac and peripheral autonomic neuropathy. *Diabetes Care* 2005; 28: 1959-64
 19. Bytzer P, Talley NJ, Jones MP, Horowitz M. Oral hypoglycemic drugs and gastrointestinal symptoms in diabetes mellitus. *Aliment Pharmacol Ther.* 2001; 15:137-42.
-
-
-