Does Diabetic Microvascular Complications Affect Gastrointestinal Symptoms?

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Abstract- Due to high prevalence of diabetes in our region (16.3%) and no data on the frequency of gastrointestinal (GI) symptoms in this population, we performed a cross-sectional study to evaluate the frequency of GIsymptoms in diabetic patients and its association between microvascular complications (retinopathy and nephropathy) and gastrointestinal symptoms in diabetic subjects.This analytical cross-sectional study was conducted from 2014 to 2016 on 233 patients with type 2 diabetes mellitus (T2DM), 30-65-year, referred to Yazd diabetic research center. They were selected by convenient sample method. A questionnaire according to Rome III Criteria was used to collect digestive information related to diabetes. Last HbA1c (Since 2-3 months ago) was available in the patient's medical folder. Diabetic nephropathy defines to increased excretion rate of albumin in the urine in the range of above 30 mg/g creatinine. Diabetic retinopathy was examined by an expert ophthalmologist (retinal specialist). For the current study, 233 patients (age 30-65 years with mean age of 57.43±10.49 years, 102 (43.8%) males and 131 (56.2%) females) were included. Among 233 patients, 91 cases (39.1%) had nephropathy,and 111(47.6%) subjects had different degrees of retinopathy. Bloating and early satiety and upper GI symptoms were higher in the subjects with retinopathy than another group. In summary, this study provides evidence that GI symptoms in diabetic subjects are independently linked to diabetic complications, particularly to retinopathy.

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Introduction

Diabetes mellitus (DM) as a chronic disease affecting many people worldwide and the incidence rises to 439 million adults by 2030 (1). Microvascular complications of diabetes such as nephropathy and retinopathy cause mortality and morbidity in diabetic patients (2). Oxidative stress, caused by the overproduction of reactive oxygen species (ROS) plays an important role in the activation of other pathogenic pathways involved in diabetic complications, including elevated polyol pathway activity, non-enzymatic glycation, and PKC levels which in turn lead to the development of micro-and macro-vascular complications (3).

Gastrointestinal (GI) complications of diabetes have become more common as the prevalence and duration of diabetes increased, andthesesymptoms include esophagealdysmotility, gastroparesis, enteropathy (4). Diabetes represents a state of high oxidative stress as a result of hyperglycemia-inducedROS generation. The etiology of gastrointestinal dysfunction still remains unclear, but oxidative stress appears to be an important player in gastrointestinal complications of diabetes specifically diabetic gastroparesis (5).

Interstitial cells of Cajal and the enteric nervous system appear to be the most significantly affected cell types in diabetes, though autonomic neuropathy and smooth muscle dysfunction have also been well described and more recently immune cells have been recognized as important players (6).

GI symptoms in diabetes are associated with poor glycemic control but not to the duration of diabetes or type of treatment in one study (7). Also, GI symptoms in diabetes mellitus may be linked to diabetic complications, particularly peripheral neuropathy, and to poor glycemic control but not directly associated with the duration of diabetes (8). Several studies have described an association between retinopathy and gastrointestinal dysmotility (9,10).

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Due to the high prevalence of diabetes in our region (16.3%) and no data on the frequency of GI symptoms in this population (11), we, therefore, performed a cross-sectional study to evaluate the association between microvascular complications (retinopathy and nephropathy) and GI symptoms in diabetic subjects.

Materials and Methods

Study population and data collection

This analytical cross-sectional study was conducted from 2014 to 2016 on 233 patients with type 2 diabetes mellitus (T2DM), 30-65 years, referred to Yazd diabetic research center. They were selected by convenient sample method. Exclusion criteria were patients with glomerular filtration rate (GFR) less than 60, hypothyroidism, current smoker or any illicit drugs, history of abdominal surgery, inflammatory bowel disease (IBD), celiac disease, cardiac failure class III and IV. Also, patients who consume anticholinergic drugs, H2 blockers,and proton pump inhibitors were excluded from the study.

Demographic data and medical history were collected by the researcher. A questionnaire according to Rome III Criteria was used to collect digestive information related to diabetes (12). HbA1c was checked in Yazd diabetic research laboratory. Diabetic nephropathy was defined asincreased excretion rate of albumin in the urine in the range of above 30mg/g creatinine (13). All patients with diabetic nephropathy were checked by a nephrologist. Ophthalmologic examination including visual acuity (by means of Snellen charts), intraocular pressure (using Applanation Tonometry), fundoscopy (utilizing slit lamp and non-contact lenses) and indirect ophthalmoscopy were also completed. All the relevant examinations were completed by an ophthalmologist. Based on their optic fundi findings, they were classified into two major groups: with and without retinopathy .

Finally, frequency of GI symptoms in patients with and without nephropathy, retinopathy and one of the microvascular complications were compared .

Research ethics

This research was presented to the ethics committee of ShahidSadoughi University of Medical Sciences and approved by the internal medicine department. The ethics committee approved the study with the number IR.SSU.REC.MEDICINE.REC.1394.388. The patients were informed about the objective and nature of the study, and each participant provided written consent prior to the study.

Statistical analyses

The sample size was calculated by comparison of two proportion according to α=0.05 and β=0.2. Data analysis was performed using SPSS software Version 22. Data were reported as mean±standard deviation (SD) or frequency (%) and independent T-test, One Way ANOVA, *Chi*-Square and Spearman correlation coefficient tests were used. A *P* less than 0.05 was considered as statistically significant.

Results

For the current study, 233 patients (age 30-65 years with mean age of 57.43±10.49 years, 102 (43.8%) males and 131 (56.2%) females) were included.

Among 233 patients, 91 cases (39.1%) had nephropathy,and 111(47.6%) subjects had different degrees of retinopathy. The mean age of subjects with microvascular complications was 58.92±0.78 and in the other group was 54.22±1.27 (*P*=0.02). The mean of HbA1c in patients with microvascular complications was 8.07±0.12 and 7.65±0.24 in patients without microvascular complications (*P*=0.129). Diabetes duration in patients with microvascular complications was 12.29±0.67 years and in the subjects without microvascular complications was 6.01±0.72 years (*P*=0.001). Distribution of GI symptoms in individuals with and without nephropathy is presented in table 1.

Also, the distribution of GIsymptoms in individuals with and without retinopathy is showed in table 2. Bloating and early satiety and upper GI symptoms were higher in the subjects with retinopathy than another group.

The regression model was used to evaluate the effect of the variables such as age, duration of diabetes and HBA1C on gastrointestinal symptoms among T2DM patients. The results of this test showed that the change in age, duration of diabetes and HbA1c does not affect the frequency of gastrointestinal symptoms (Table 3).

Table 1. Distribution of gastrointestinal symptoms in type 2 diabetic patients with respect to nephropathy

Nephropathy	With		Without		*P*
	Frequency n=91	Percent 39.1%	Frequency n=142	Percent 60.9%	
Bloating	35	38.4	78	55	0.01
Postprandial Fullness	28	30.7	36	25	0.225
Early satiety	18	19.7	34	24	0.027
Nausea	6	6	17	12	0.0127
Heartburn	25	27.4	45	31.7	0.248
Upper Abdominal Pain	24	26	36	25	0.502
Gas Passing	21	23	35	24.6	0.456
Diarrhea	7	7.6	10	7	0.519
Constipation	47	51.6	54	38	0.023
Intermittent Diarrhea and Constipation	1	1.1	5	3.5	0.026
Upper digestive symptoms	79	86.8	121	85	0.37
Lower digestive symptoms	76	83	121	85	0.625

Table 2. Distribution of gastrointestinal symptoms in type 2 diabetic patients with respect to retinopathy

Retinopathy	With		Without		*P*
	Frequency n=111	Percent 47.6%	Frequency n=122	Percent 52.4%	
Bloating	60	54	53	43.4	0.048
Postprandial Fullness	31	27.9	33	27	0.498
Early satiety	31	27.9	21	17.2	0.033
Nausea	9	8	14	11.4	0.269
Heartburn	35	31.5	35	28.6	0.668
Upper Abdominal Pain	26	23	34	27.8	0.28
Gas Passing	30	27	26	21.3	0.193
Diarrhea	6	5.4	11	9	0.22
Constipation	50	45	51	41.8	0.33
Intermittent Diarrhea and Constipation	4	3.6	2	1.6	0.298
Upper digestive symptoms	95	85	93	76	0.004
Lower digestive symptoms	94	84	1.3	84.4	0.276

Table 3. The logistic regression findings of the variables on gastrointestinal symptoms among type 2 diabetic patients

Variables	Odds ratio	*P*
Age	1.019 (0.706-1.19)	0.766
Duration of the disease	1.009(0.484-1.76)	0.897
HBA1C	1.27(0.982-1.47)	0.078

Discussion

Oxidative stress plays an important role in the pathogenesis of diabetic complications, which in turn lead to the development of micro and macro-vascular complications (3).

Also in GI tracts, oxidative stress appears to be an important role in diabetic l complications specifically gastroparesis (5).

Our study was set out to evaluate the association between microvascular complications and GI symptoms in diabetic subjects.

Constipation was higher than in persons with nephropathy than without nephropathy.

Damage to the myenteric nerve plexus due to autonomic neuropathy and fibrosis of the intestinal muscular layers result in stasis of the intestinal contents. Reduced bowel motility results in constipation that may lead to overflow incontinence. Bacterial overgrowth is a consequence of intestinal stasis (14). Neuropathy and nephropathy are chronic microvascular complications due to longstanding hyperglycemia. Therefore it is possible to seek a higher rate of constipation in nephropathic subjects. People with nephropathy use higher medication for treatment of nephropathy than subjects without renal involvement, so attention to drug history of persons is important because of some medication maybe potential cause of constipation in this group (15).

Bloating, early satiety and upper digestive symptoms were higher than in persons with retinopathy than without retinopathy. These results are in agreement with previous studies (9,10). In the mentioned studies, there was a strong association between gastroparesis and

esophageal dysmotility with retinopathy but no nephropathy. The etiology of this association between GI symptoms and retinopathy may not be due to the longer duration of diabetes in the subjects with GI symptoms group, because the prevalence of GI symptoms except constipation in patients with and without nephropathy was not differing. Also using logistic regression analysis and adjusting for factors such as age, duration of diabetes and HBA1C, it seems that gastrointestinal symptoms are independently associated with diabetic retinopathy.

Increased HbA1c levels are associated with a high rate of GI symptoms (7,8,16). But the mean HbA1c in our study was similar in two groups. HbA1c is a poor marker for daily glucose variations. We did not check fasting blood sugar (FBS) at the time of the study, and while the HbA1c level serves as a surrogate for overall blood glucose control, it does not accurately reflect the state of blood sugars in patients at the time of their study. Conversely, a patient with wide variation in blood sugars may have a normal HbA1c level, and while this is a predictor of overall morbidity in diabetic patients, it may underestimate the importance of fluctuations of glucose levels in these patients (17). Although increasing HbA1c levels are associated with high rate of GI symptoms (7,8), the fact that in our study, GI symptoms were significantly different despite similar HbA1c levels supports the concept of association between GI symptoms and retinopathy.

Limitation of our study was small sample size. Also, we used a subjective method for evaluation of GI symptoms, prospective studies with large sample size and with an objective procedure such as esophageal and anorectalmanometry and gastric emptying scintigraphy may be helpful.

In summary, this study provides evidence that GI symptoms in diabetic subjects are independently linked to diabetic complications, particularly to retinopathy.

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