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Increased gastrointestinal symptom frequency in diabetes mellitus even with good glycemic control

Glisemik kontrol sağlanan diabetes mellitus hastalarında artmış gastrointestinal semptom sıklığı

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ABSTRACT

Background and **Aim:** Gastrointestinal problems are reportedly more frequent in patients with diabetes mellitus (DM) compared to the general population and are a cause of reduced quality of life (QOL). Even though studies have suggested that parameters such as glycemic control and disease duration are responsible for upper gastrointestinal (GI) symptoms in DM, there is little compelling evidence to show a direct relationship given the fact that various other studies report no relationship. These conflicts may be caused by the lack of standardization of patient populations, evaluation methods, and other causes. Our aim was to determine and compare the frequency of GI symptoms and GI-related QOL in recently diagnosed DM patients and healthy controls in order to evaluate this relationship with the minimization of confounding factors.

Material and Method: A total of 59 patients newly diagnosed with DM and 92 age-and sex-matched controls were included in this study. Demographic characteristics, chronic diseases, GI symptoms (as measured by 8-MGSI score) and GI-related QOL (irritable bowel syndrome quality of life, IBS-QOL) scores were evaluated. Linear regression analysis was performed to determine factors that independently influenced IBS-QOL.

Results: The patient and control groups were similar with regard to all characteristics except for chronic diseases. The scores for 8-MGSI and IBS-QOL were significantly worse in patients with DM. Regression analyses showed that IBS, DM, and dyspepsia were independent factors that influence IBS-QOL scores.

Conclusion: The results of our study show that the effect of DM on GI symptoms is not a function of disease duration or glycemic control; DM presence itself seems to have adverse effects on the GI system through mechanisms that are yet unknown. The explanation of these mechanisms relies on experimental research and prospective studies with rigid patient inclusion criteria.

Keywords: Diabetes mellitus, gastrointestinal tract pathology, irritable bowel syndrome, quality of life

ÖZ

Amaç: Gastrointestinal problemlerin, diabetes mellitus (DM) olan hastalarda, genel popülasyona göre daha sık olduğu ve yaşam kalitesinde azalmalya neden olduğu bildirilmektedir. Çalışmalar, glisemik kontrol ve hastalık süresi gibi parametrelerin DM'deki üst gastrointestinal semptomlardan sorumlu olduklarını ileri sürmelerine rağmen, bazı çalışmaların da hiçbir ilişki olmadığını bildirdiği gerçeği göz önüne alındığında doğrudan bir ilişki olduğunu gösteren çok az kanıt vardır. Bu çatışmalar, hasta popülasyonlarının standart olmamasından, değerlendirme yöntemlerinden ve diğer nedenlerden kaynaklanabilir. Amacımız yakın zamanda tanı almış DM hastalarında ve sağlıklı kontrollerde gastrointestinal semptomlarının sıklığını ve gastrointestinal semptomlar ile ilişkili yaşam kalitesini belirlemek ve karşılaştırmak, bu faktörlerin en aza indirgenmesini değerlendirmektir.

Gereç ve yöntem: Çalışmaya DM tanısı konmuş toplam 59 hasta, 92 yaş ve cinsiyet uyumlu kontrol grubu dahil edildi. Demografik özellikler, kronik hastalıklar, GI semptomları (8-MGSI skoru ile ölçülen) ve irritabl barsak sendromu yaşam kalitesi(IBS-QOL) skorları değerlendirildi. IBS-QOL'ü bağımsız olarak etkileyen faktörleri belirlemek için doğrusal regresyon analizi yapıldı.

Bulgular: Hasta ve kontrol grubu kronik hastalıklar dışındaki tüm özellikler açısından benzerdi. DM'li hastalarda 8-MGSI ve IBS-QOL skorları anlamlı olarak daha kötüydü. Regresyon analizleri İBS, DM ve dispepsinin IBS-QOL skorlarını etkileyen bağımsız faktörler olduğunu gösterdi.

Sonuç: Çalışmamızın sonuçları, DM'nin gastrointestinal semptomlar üzerindeki etkisinin hastalık süresinin veya glisemik kontrolden etkilemediğini göstermektedir; DM'nin varlığı, henüz bilinmeyen mekanizmalar yoluyla gastrointestinal sistem üzerinde olumsuz etkilere sahiptir. Bu mekanizmaların açıklaması için hasta dahil etme kriterleri daha kesin olarak belirlenmiş deneysel çalışmalara ihtiyaç vardır

Anahtar Kelimeler: Diabetes mellitus, gastrointestinal sistem patolojisi, irritabl barsak sendromu, yaşam kalitesi

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INTRODUCTION

According to International Diabetes Federation, there were 451 million patients with diabetes mellitus (DM) diagnosis in 2017, and it was estimated that this number would increase to 693 million patients by the year 2045; even though it is estimated that about half of all people living with diabetes are undiagnosed. In 2017, around 5 million deaths worldwide occurred due to DM (1). Diabetes mellitus is a complex chronic disease that requires continuous medical care with multifactorial risk reduction strategies that go beyond glycemic control, in order to maintain quality of life, control risks, manage disease symptoms, and reduce complications (2).

The relationship between DM and gastrointestinal diseases has not been fully elucidated (3). According to a small number of studies, DM patients are believed to be at enhanced risk for various problems of the gastrointestinal (GI) system, including gastric problems, deficiencies in motility, and it was also stated that the frequency of GI symptoms including abdominal pain, acid regurgitation, abdominal fullness after meals and dysphagia was higher among those with DM (4-7). Although the underlying mechanism of the association between DM and GI symptoms remains unknown, currently, the best explanation to this relationship may be the neuropathic effects of diabetes which encompass the GI tract (8). This is backed by reports that have suggested an association between GI symptoms and disease duration in patients with type 2 DM (9). Furthermore, it is known that constipation, diarrhea and inflammatory bowel diseases are more frequently seen in patients with DM (10).

However, to our knowledge, there are only a few studies assessing this topic and there have been no attempts to investigate whether a relationship between irritable bowel syndrome (IBS) and DM exists. Also, the gastrointestinal problems of newly-diagnosed diabetic patients with good blood glucose control have not been studied before. Therefore, the determination of the frequency and severity of upper GI symptoms using the Dyspepsia Severity Index of the Mean Global Severity Index (8-MGSI) among patients with DM may provide valuable data for increasing the quality of care provided to patients with DM. In this study, we structured our research on two main research questions: I. Are there any differences between patients with and without diabetes in terms of upper GI symptoms and IBS? II. Does having DM influence IBS-related quality of life (QOL)?

MATERIAL AND METHOD

Study Group and Design

The study was performed by the inclusion of a total of 151 individuals who applied to the outpatient clinic, of Internal Medicine from (March-June 2014). The patient group was comprised of 59 patients who were recently diagnosed with Type 2 DM and did not have any complications associated with the disease. The control group was comprised of consecutively selected, age-and sex-matched individuals without chronic medication use who applied to our department within the study duration and also did not have any systemic diseases such as hypertension (HT), coronary artery disease (CAD), chronic obstructive pulmonary disease (COPD) and cerebrovascular disease (CVD). In the patient group, those who had a history suggesting the presence of complications associated with DM were also excluded. The inclusion of patients into the control group was performed consecutively, but according to the current age and sex distribution of the patient group at that moment. These distribution assessments were performed weekly; therefore, the inclusion of patients that would significantly alter the age and sex distribution of groups was prevented.

Ethical Declaration

Participation in the study was purely based on volunteering; thus, all individuals provided written informed consent for the study indicating their volunteer status. The study was begun after obtaining approval from the Clinic Research Ethics Board. (18 Mart University Medical School **14.12.2013**, EK-2013-32)

Measurements

In patients included in the patient group, the presence of DM was confirmed according to WHO criteria. The medical history, smoking status and alcohol use of all individuals included in the study were assessed and recorded. Those who smoked at least 1 cigarette per day were defined as smokers, while those drinking at least 30 ml's of alcohol per week were defined as alcohol users. Disease duration and drug use were recorded in the patient group, and all individuals' height and weight were measured. Patient's IBS diagnoses and the determination of dyspepsia presence/absence were based on the Rome III diagnostic criteria. For the measurement of dyspepsia, the Dyspepsia Severity Index of the Mean Global Severity Index (8-MGSI) by De Luca and colleagues was used (11). In this tool, the severity and frequency of complaints are measured on a scale of 1 to 5 and the scores for each section are calculated by multiplying these two values.

The IBS-related QOL of patients was measured via the Irritable Bowel Syndrome Quality of Life (IBS-QOL) questionnaire (12). In this scale, each question is answered on a 5-level Likert scale and a higher score indicates worse QOL. The subscales are defined and measured as follows: Questions 1, 6, 7, 9, 10, 13, 16 and 30 measure dysphoria, questions 3, 18, 19, 22, 27, 29 and 31 measure body image, questions 5, 21, 25 and 26 measure food avoidance, questions 4, 15 and 32 measure sexual status, questions 11, 23, and 28 measure activity interference, questions 2, 14, 17 and 34 measure health concerns, questions 12 and 20 measure social reaction, and questions 8, 24 and 30 measure family relationship. The total score is obtained by adding all subscale scores.

Statistical Analysis

All data obtained during the study were transferred to the SPSS software for Windows, version 21.0 (IBM, Armonk, NY, USA). Categorical data were given as frequency (n) and percentage, while continuous data were given by means and standard deviations (SD). The normality of distribution of continuous variables was tested with the Shapiro Wilk test. In variables where normal distribution and parametric criteria were met, the Student's t-test was used for comparison, while the Mann Whitney *U* test was used in non-normal distributions. To determine factors that influenced IBS-QOL, we used a linear regression model which accepted the IBS-QOL score as the dependent variable. All parameters with a p value lower than 0.05 in single-variable tests were tested as independent variables. A p value lower or equal to 0.05 was defined as the levels of statistical significance.

RESULTS

Among the 59 patients with DM (31 males) and 92 controls (51 males), the mean ages were 52.08 ± 11.42 and 53.49 ± 9.3 years, respectively. The demographic characteristics and medical history findings of groups were similar except for CAD, HT, hyperlipidemia and dyspepsia frequencies which were significantly higher in the patient group (**Table 1**).

Table 1. Summary of Individuals' Characteristics with regard to groups

	Controls	Patients	Total	P
N	92	59	151	N.A
Age	53.49 ± 9.30	52.08 ± 11.42	52.94 ± 10.16	0.430
Gender (Male)	51 (55.43%)	31 (52.54%)	82 (54.3%)	0.857
Height (cm)	168.75 ± 8.43	166.34 ± 7.82	167.81 ± 8.25	0.080
Weight (kg)	77.5 (48-110)	80 (50-145)	78 (48-145)	0.085
Smoker	19 (20.65%)	14 (23.73%)	33 (21.85%)	0.807
Alcohol User	17 (18.48%)	13 (22.03%)	30 (19.87%)	0.745
Coronary Artery Disease	0 (0.00%)	4 (6.78%)	4 (2.65%)	0.022
Hypertension	0 (0.00%)	18 (30.51%)	18 (11.92%)	<0.001
COPD	0 (0.00%)	1 (1.69%)	1 (0.66%)	0.391
CVD	0 (0.00%)	2 (3.39%)	2 (1.32%)	0.151
Hyperlipidemia	0 (0.00%)	6 (10.17%)	6 (3.97%)	0.003
PPI User	6 (6.52%)	8 (13.56%)	14 (9.27%)	0.243
Dyspepsia	31 (33.70%)	32 (54.24%)	63 (41.72%)	0.020
IBS	10 (10.87%)	11 (18.64%)	21 (13.91%)	0.269

Data are given as mean ± standard deviation or median (minimum-maximum) for continuous variables regarding normality of distribution, and frequency (percentage) for categorical variables
COPD: Chronic obstructive pulmonary disease CVD: Cerebrovascular disease: PPI: Proton pump inhibitors IBS: İrritable bowel syndrome

When patients with DM were analyzed for glycemic control, it was found that median blood glucose was 110 (min-max: 100–155) mg/dL and mean hemoglobin A1c levels were 5.66 ± 0.38%. When the scores obtained from the 8-MGSI scale were compared between groups, we found that patients with DM had significantly higher scores for the following parameters: epigastric pain, abdominal discomfort or pain, upper abdominal fullness and discomfort, heartburn, and acid regurgitation (**Table 2**).

Table 2. Summary of Dyspepsia Severity Index of the Mean Global Severity Index Scores (8-MGSI) regarding groups

	Controls	Patients	Total	P
Epigastric pain	2.59 ± 3.11	5.05 ± 6.13	3.55 ± 4.68	0.012
Pain severity before meals or when hungry	2.66 ± 3.70	2.93 ± 4.85	2.77 ± 4.17	0.668
Pain relieved by eating or antiacid use	2.82 ± 4.12	3.15 ± 4.52	2.95 ± 4.27	0.305
Abdominal discomfort or pain	2.35 ± 3.41	4.42 ± 5.67	3.16 ± 4.53	0.010
Upper abdominal fullness	2.53 ± 3.88	6.97 ± 8.09	4.26 ± 6.26	<0.001
Upper abdominal discomfort	2.14 ± 3.04	6.1 ± 7.04	3.69 ± 5.34	<0.001
Heartburn	2.01 ± 3.11	3.27 ± 4.63	2.50 ± 3.82	0.008
Acid regurgitation	1.63 ± 2.06	2.68 ± 4.11	2.04 ± 3.06	0.009
Total Score	2.34 ± 2.39	4.32 ± 4.26	3.12 ± 3.38	<0.001

Data given as mean ± standard deviation

In regard to IBS-QOL scores, patients with DM were also found to have significantly higher (worse) scores in all subscales (**Table 3**).

Table 3. Summary of irritable bowel syndrome quality of life (IBS-QOL) Scores Regarding Groups

Original subscale	Controls	Patients	Total	P
Dysphoria	8 (4-28)	9 (8-33)	8 (4-33)	<0.001
Body image	4 (4-14)	5 (4-16)	4 (4-16)	<0.001
Food avoidance	3 (3-11)	3 (3-14)	3 (3-14)	<0.001
Sexual	2 (2-7)	2 (2-9)	2 (2-9)	0.002
Interference with activity	7 (7-24)	9 (7-27)	7 (7-27)	<0.001
Health worry	3 (3-14)	4 (3-14)	3 (3-14)	<0.001
Social reaction	4 (4-14)	5 (4-15)	4 (4-15)	<0.001
Relationship	3 (2-10)	3 (3-14)	3 (2-14)	0.002
Total	34 (34-115)	41 (34-135)	34 (34-135)	<0.001

Data given as median (minimum maximum)

Linear regression analysis with IBS-QOL score as the dependent variable revealed that IBS, DM and dyspepsia were independent factors that influenced IBS-QOL score (**Table 4**).

Table 4. Linear Regression Model with irritable bowel syndrome quality of life (IBS-QOL;) Scores as Dependent Variables

	Unstandardized Beta Coefficients (β)	Standard Error	Standardized Coefficients	T	P	95.0% Confidence Interval for	
(Constant)	32,857	1,878		17,492	<0.001	29,145	36,570
IBS	25,547	3,983	0.431	6,413	<0.001	17,675	33,419
DM	11,404	2,693	0.272	4,234	<0.001	6,082	16,727
Dyspepsia	8,892	2,838	0.214	3,134	0.002	3,284	14,500

R2 = 0.409 ; F = 35.661 ; p < 0.001
IBS: İrritable bowel syndrome DM: Diabetes mellitus

DISCUSSION

In the current study, although the frequency of IBS was similar in the patient and control groups, having DM was found to significantly worsen IBS-QOL score. This was an interesting finding, as our patient group was comprised of patients with good glycemic control and newly diagnosed DM; thus the possibility of adversities caused by long-standing DM was minimal, indicating that the mechanisms leading to an increase in GI symptoms among patients with type 2 DM are not fundamentally associated with the chronic effects of the disease (6).

To date, a significant body of evidence has suggested that hyperglycemia may increase the perception of GI symptoms (13-17), while others have associated disease duration with increased frequency of GI symptoms (9,18). However, in studies involving patient follow up and corrections for depressive symptoms, disease duration, general quality of life and other factors, the relationship between GI symptoms and diabetes does not seem to be very compelling (19-22). Furthermore, in an earlier study performed among middle-aged individuals with DM (similar to our patient group), no increase was found in GI symptoms when patients were compared to the general population (5). These conflicts in results and findings may have reliable and accurate explanations involving the evaluation method of GI symptoms, the use or absence of scoring systems, and many other factors including the differences in populations, patient characteristics, medication type/adherence, and glycemic control.

In the current study, we compared dyspepsia, IBS-QOL and 8-MGSI scores among patients with DM and controls. The results showed that dyspepsia was more frequent among patients, while IBS frequencies were similar to controls. However, the majority of 8-MGSI subscale scores (except for pain severity when hungry and pain relief with eating or antiacids) was increased among patients with type 2 DM. In a recent and detailed review of the literature, DM was reported to be a cause of dysphagia, gastroesophageal reflux, bloating, early satiety, nausea, upper abdominal pain, delayed gastric emptying, accelerated/slow intestinal passage, malabsorption and slow colonic transit (23). Even so, the different methodologies used in these studies and the differences in the characteristics of patients cause limitations in overall data assessment for the purpose of identifying a link between DM and GI symptoms. These limitations may be circumvented with specific study designs and conduct of studies involving strict limitations in patient inclusion. For instance, in a study by Ghadiri-Anari and colleagues (24), in which pre-diabetic patients were compared with healthy controls, the frequency of heartburn, nausea, bloating, early satiety, gas passage, and constipation were found to be significantly higher among pre-diabetics. This study design completely eliminates the possible effects of medications such as metformin on the frequency of GI symptoms; therefore enabling a much better comparison. Similar to this study, we aimed to prevent the chronic complications of DM from affecting GI symptoms by including recently diagnosed patients and our results showed that, even though the frequency of IBS was similar among our study groups, patients with type 2 DM had worse clinical experiences with GI symptoms as measured by 8-MGSI.

The comparison of IBS-QOL scores showed that patients with DM had significantly worse IBS-related QOL in the current study. Similarly, in a study by Zetina-Lopez et al. (25), DM patients with GI symptoms were found to have significantly reduced QOL compared to DM patients without GI symptoms, which is supported by a review on this topic that concluded GI symptoms had a significant influence on QOL. The authors even suggested that the treatment of GI symptoms should be made a priority to increase QOL in patients with DM (26). The number of GI symptoms have also been associated with a worsening in health-related QOL scores in patients with both type 1 and type 2 DM; however, the reduction in QOL was reportedly more evident in those with type 2 DM (27).

The current study is different from previous studies assessing QOL with regard to GI symptoms in patients with DM for the fact that we evaluated QOL with a scoring system that was directly associated with GI complaints and symptoms. This approach may be a way to show a more direct relationship between DM and its effects on GI symptoms due to the lack of questions associated with other health dimensions that may reduce scores obtained with overall QOL questionnaires. In the current study, all dimensions of the IBS-QOL questionnaire were worse among patients who had been recently diagnosed with DM. Similar findings have been reported in various studies involving different groups of DM patients in terms of disease duration, type and use of medications and glycemic control. However, our study suggests that DM causes an increase in 8-MGSI and IBS-QOL scores even when duration with DM is low and glycemic control, as measured by HbA1c, is rather good.

In our study, in order to minimize the effects of disease duration and glycemic control on upper GI symptoms, we included patients with recently diagnosed type 2 DM. However, anti-diabetic drugs are known to have GI tolerability issues (28), which may be a confounding factor in

our analyses. Although this is an important limitation, a similar study in pre-diabetic patients also reported an increase in GI symptoms (24), suggesting that DM causes GI symptoms even without drug use and before the definite development of the disease.

CONCLUSION

Our findings demonstrate a relationship between DM presence and GI-related symptoms and also IBS-QOL scores. Despite various studies suggesting a neuropathic link between GI symptoms and DM, our results suggest that DM adversely influences the GI system even when recently diagnosed and in the presence of good glycemic control. We believe current explanations that attribute DM-associated GI problems to chronic developments and complications are not sufficient, and further experimental research or clinical studies with prospective designs with very specific inclusion criteria are required to elucidate the underlying mechanisms of this relationship.

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Ethical approval: All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all individual participants included in the study.

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