

Prevalence of gastro-esophageal reflux in diabetic patients at a tertiary hospital in Central Saudi Arabia

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ABSTRACT

الأهداف: قياس نسبة انتشار الارتجاع المعدي المريئي في مرضى السكري والعوامل المرتبطة به وعلاقته بوجود مضاعفات السكري.

المنهجية: أجريت دراسة مقطعية عرضية لاستقصاء نسبة الارتجاع المعدي المريئي في مرضى السكري خلال شهري يناير وفبراير من عام 2019 وذلك بجمع استبانات خاصة بتشخيص مرض الارتجاع المعدي المريئي والتي تم إكمالها من قبل 403 من مرضى السكري في العيادات الخارجية في مستشفى مرجعي للرعاية الصحية الثالثة.

النتائج: انتشار الارتجاع المعدي المريئي بين مرضى السكري كان بنسبة 44.9%. كما أظهرت الدراسة انتشار أعلى لمرض الارتجاع في: الإناث ($p < 0.001$)، والأشخاص الأكبر سناً ($p = 0.038$)، ومن لديهم معدل كتلة جسم عالية ($p = 0.006$). كانت نسبة المرضى المدخنين من بين الفئة المصابة بالارتجاع 1.7% وهي أقل من المدخنين في الفئة الغير مصابة بالارتجاع ($p = 0.007$). وعند مقارنة مضاعفات السكري بين مرضى الارتجاع المعدي المريئي مع المرضى السليمين وجدت زيادة في مضاعفات السكري التالية: تنميل الأطراف ($p = 0.023$) واعتلال الكلى ($p = 0.041$) عند مرضى السكري المصابين بالارتجاع. بينما كانت نسبة جلطات القلب ($p = 0.038$) أعلى في مرضى السكري السليمين من الارتجاع المعدي المريئي. عند استخدام تحليل الانحدار اللوجستي، أظهرت النتائج أن العوامل المستقلة المرتبطة مع مرض الارتجاع المعدي المريئي هي كون المريضة أنثى ($p = 0.013$)، والفئة العمرية الأعلى من 65 سنة ($p = 0.007$).

الخلاصة: ينتشر الارتجاع المعدي المريئي بين مرضى السكري بنسبة عالية تصل إلى 45%. العوامل المؤدية إلى زيادة انتشاره هي: كون المريض أنثى، وتقدم العمر إلى أعلى من 65 سنة. وأظهرت النتائج عدم وجود علاقة مع العوامل الأخرى (معدل كتلة الجسم، التدخين، مدة الإصابة بمرض السكري، الخطة العلاجية، وجود مضاعفات السكري).

Objectives: To estimate the prevalence of gastro-esophageal reflux disease (GERD) among diabetic patients and to investigate GERD's potential association with diabetic complications, and patients' sociodemographic and clinical characteristics.

Methods: This cross-sectional study used the GERD questionnaire (GerdQ) in 403 diabetic patients attending the outpatient clinics at King Khalid University Hospital, King Saud University Medical City, King Saud University; a tertiary hospital in Riyadh, Saudi Arabia, between

January and February 2019. On the basis of a cutoff GerdQ score of 8, we distinguished GERD and non-GERD groups.

Results: Gastro-esophageal reflux disease prevalence was 44.9%. Of the diabetic patients with GERD, 76.8% were female ($p < 0.001$). Gastro-esophageal reflux disease patients were older (mean age: 55.27, $p = 0.038$) and had a slightly higher body mass index (BMI) than non-GERD (32.04 versus, 30.20 $p = 0.006$), respectively. Smokers in the GERD group were 1.7% versus 7.2% in the non-GERD group ($p = 0.007$). Peripheral numbness ($p = 0.023$) and nephropathy ($p = 0.041$) were more prevalent in patients with GERD, while myocardial infarction was more prevalent in non-GERD subjects ($p = 0.038$). On multi variable analysis, the only independent GERD risk factors were female gender ($p = 0.013$) and age > 65 years ($p = 0.007$).

Conclusion: Gastro-esophageal reflux disease prevalence in diabetic patients was 45%. Diabetic patients with GERD were more often female and older > 65 years. None of the other tested factors (BMI, smoking status, diabetes mellitus duration, therapeutic plan, or diabetic complications) showed significant difference between GERD and non-GERD groups.

Keywords: diabetes mellitus, gastroesophageal reflux, diabetes mellitus/complications, gastrointestinal motility, Saudi Arabia/epidemiology

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Diabetes mellitus (DM) is a leading cause of several gastrointestinal motility disorders, that includes gastro-esophageal reflux disease (GERD) and gastroparesis.^{1,2} Obesity is a common factor in type 2 DM patients. The mechanism of GERD development in diabetic patients is multifactorial and mainly directed by obesity and gastro-esophageal dysmotility that together or alone can result in GERD. The presence of obesity in those patients creates a high intraabdominal pressure that may result in hiatal herniation which is a direct anatomical cause of reduction of lower esophageal sphincter tone causing acid reflux. The other pathway of GERD development is caused by gastroparesis and esophageal dysmotility resulting from neuropathy that complicates hyperglycemia and DM. Furthermore, the presence of diabetes or obesity causes hormonal dysregulation of ghrelin and motilin. This hormonal dysregulation also contributes to gastroparesis and esophageal dysmotility.¹ In addition to carrying the risk of Barrett's esophagus and esophageal adenocarcinoma, GERD negatively affects patients' living conditions, productivity, and sleep.^{3,4} Nevertheless, modification of lifestyle habits such as reducing meal size and controlling blood sugar levels can prevent and treat gastrointestinal complications of DM.²

The prevalence of type 2 DM in the Kingdom of Saudi Arabia (KSA) is 32.8%.⁵ The incidence of new cases of type one DM among age group of 0-14 years in KSA in 2019 is 31.4 per 100,000 population per year.⁶

Gastro-esophageal reflux disease is also common in the general population of KSA, with a prevalence varying between 28.7-45.4%.^{7,8} Several studies in other countries have reported more GERD prevalence in patients with DM than in the general population.^{9,10}

In this study, we aimed to estimate the prevalence of symptomatic GERD in diabetic patients and to investigate GERD's potential associations with diabetic microvascular and macrovascular complications, and with patients' sociodemographic and clinical characteristics.

Methods. We conducted a PubMed search using the medical subject heading terms: gastroesophageal reflux, diabetes mellitus, epidemiology, diabetes mellitus/

complications, gastrointestinal motility, heartburn, and Saudi Arabia/epidemiology as well as keyword searches of Saudi Arabia, prevalence, GERD, diabetic. We also manually searched reference citations in the identified articles. We reviewed studies in the English language only.

We conducted this cross-sectional study in the outpatient clinics of King Khalid University Hospital, King Saud University Medical City, King Saud University; a tertiary hospital in Riyadh, KSA, between January and February 2019. The study was carried out in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of College of Medicine, King Saud University, Riyadh, KSA.

The inclusion criteria was self-report of being previously diagnosed with type 1 or 2 DM. Patients who were not diabetic or had a DM type other than type 1 or 2 were not invited to participate.

We collected data through a questionnaire that was completed during an interview. We explained the purpose of the study to all patients and included those who agreed to participate. We assured participants' anonymity by assigning each participant a code number for the purpose of data analysis only.

The questionnaire asked about gender, age, height, weight, smoking status, duration of diabetes, the therapeutic plan for diabetes control (diet, exercise, oral hypoglycemic agents [OHA], or insulin), and any history of micro- or macrovascular complications (numbness in extremities as a sign of peripheral neuropathy, retinopathy, nephropathy or albuminuria or proteinuria, hypertension [HTN], coronary artery disease [CAD], myocardial infarction [MI], stroke, or limb amputations). The last part was the GERD questionnaire (GerdQ) translated into Arabic. The Arabic version of GerdQ was adapted from 2 similar studies carried out in the country.^{7,8}

The GERD questionnaire, which has been shown to have a sensitivity of 65% and a specificity of 71%, is a 6-item questionnaire wherein patients were asked to recall the frequency of specific GERD symptoms during the past week. Based on the frequency, each of the 6 symptoms will account for one point on a scale of 0-3. The obtained score will range between 0-12, and GERD is diagnosed on the basis of a score of 8 or higher.¹¹

Before the study, we conducted a pilot trial on 19 diabetic patients by interviewing them face-to-face to ensure their understanding of the questions and to calculate the study sample size using the estimated proportion from the pilot study. The prevalence of GERD symptoms among the pilot study patients was 52.6%.

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We calculated the minimum sample size to be 384 by applying the following formula:

$$n = \frac{P(1-P) \times Z_{1-\alpha}^2}{d^2}$$

assuming a prevalence of 52% from the pilot study, at a 5% error rate and 95% confidence interval. We recruited 403 consecutive patients from the outpatient clinics and who reported that they had type 1 or 2 DM.

Statistical analysis. We analyzed the data using Statistical Package for Social Studies for Windows, version 22 (IBM Corp, Armonk, NY, USA). We used descriptive statistics (numbers, percentages, mean, and standard deviation [SD]) to describe the study's outcome variables. We used the Fisher's exact and Chi-square tests for categorical variables and the t-test for continuous variables. Univariable and multivariable logistic regression analyses were performed to define which risk factors were most likely to be associated with prevalent GERD. A *p*-value of <0.05 was used to define the statistical significance of the results. We used Cronbach's alpha coefficient to test the internal consistency of the Arabic GerdQ items.

Results. The Cronbach's alpha was scored at 0.848 for overall items which reflects good reliability and internal consistency of the items in the Arabic GerdQ (Table 1).

Sociodemographic characteristics are shown in Table 2. Among the 403 self-reported diabetic patients, 126 (31.3%) were male and 277 (68.7%) female. The mean±SD age of all study participants was 53.70±13.95 years. The mean±SD BMI was 31.02±6.65. Non-smokers and ex-smokers formed the vast majority of patients (n=384, 95.3%), with current smokers constitute 19 patients (4.7%).

Based on the results of the GerdQ, the subjects were divided into 2 groups: GERD (181 subjects)

Table 1 - Reliability analysis of the overall questionnaire.

Variables	Scale mean*	Scale variance*	Cronbach's alpha*	Corrected item-total correlation
Heartburn	8.95	18.16	0.82	0.67
Regurgitation	9.13	17.97	0.80	0.74
Epigastric pain	9.08	18.28	0.82	0.66
Nausea	9.27	18.78	0.82	0.64
Sleeping difficulty	9.42	19.62	0.83	0.61
GERD medications	8.99	18.60	0.85	0.50

*if item deleted, GERD: gastro-esophageal reflux disease

and non-GERD (222 subjects), accounting for a GERD prevalence of 44.9%. Table 3 shows the comparison between the characteristics of the 2 groups. Gastroesophageal reflux disease was higher among women (*p*<0.001), and among older individuals, mean±SD age was 55.27±11.93 years in the GERD compared to 52.43±15.32 years in the non-GERD subjects (*p*=0.038). Furthermore, BMI was slightly different between the 2 groups; the mean±SD BMI was 32.04±6.6 in the GERD group and 30.20±6.6 in patients without GERD (*p*=0.006). Smoking was negatively correlated with GERD: smokers accounted for 1.7% in the GERD and 7.2% in the non-GERD groups, (*p*=0.007). The prevalence of reported peripheral numbness nephropathy was higher in the GERD group than in patients without GERD, while MI was more prevalent among non-GERD subjects (Table 4). There was no difference between GERD and non-GERD patients with regard to the duration of their DM and therapeutic plans, as well as the frequency of HTN, albuminuria, amputation, stroke, CAD, and retinopathy.

On univariate logistic regression, significant risk factors associated with GERD were found to be female gender (*p*=0.002), age >65 years (*p*=0.005), obesity (*p*=0.009), peripheral numbness (*p*=0.024), and

Table 2 - Baseline characteristics of diabetic patients (N=403).

Characteristics	Mean ± SD
Gender (male/female), n (%)	126 (31.3)/277 (68.7)
Age	53.70 ± 13.95
Weight (kg)	80.17 ± 17.13
Height (cm)	160.96 ± 9.92
Body mass index	31.02 ± 6.65
Smoking status, n (%)	
Smoker	19 (4.7)
Non-smoker or ex-smoker	384 (95.3)

Table 3 - Comparison of patient characteristics between diabetic patients with and without GERD (N=403).

Characteristics	GERD (n=181)	Non-GERD (n=222)	<i>P</i> -value
Male, n (%)	42 (23.2)	84 (37.8)	<0.001
Female, n (%)	139 (76.8)	138 (62.2)	
Age (mean±SD)	55.27 ± 11.93	52.43 ± 15.32	0.038
Weight (mean±SD)	81.71 ± 16.75	78.92 ± 17.36	0.106
Height (mean±SD)	159.88 ± 9.38	161.84 ± 10.28	0.051
BMI (mean±SD)	32.04 ± 6.60	30.20 ± 6.60	0.006
Smoking status, n (%)			
Smoker	3 (1.7)	16 (7.2)	0.007
Non-smoker or ex-smoker	178 (98.3)	206 (92.8)	

GERD: gastroesophageal reflux disease, BMI: body mass index

Table 4 - Comparison of clinical characteristics between gastroesophageal reflux disease and non-GERD diabetic patients (N=403).

Characteristics	GERD (n=181)	Non-GERD (n=222)	P-value
<i>Duration of diabetes mellitus (years)</i>			
<5	47 (26.0)	56 (25.2)	0.795
5-9	36 (19.9)	42 (18.9)	
10-14	33 (18.2)	39 (17.6)	
15-19	26 (14.4)	26 (11.7)	
≥20	39 (21.5)	59 (26.6)	
<i>Therapeutic plan</i>			
Exercise	44 (24.3)	61 (27.5)	0.471
Diet therapy	75 (41.4)	86 (38.7)	0.582
OHA	146 (80.7)	162 (73.0)	0.070
Insulin therapy	79 (43.6)	110 (49.5)	0.238
<i>Diabetic complications</i>			
Peripheral numbness	125 (69.1)	129 (58.1)	0.023
Hypertension	89 (49.2)	97 (43.7)	0.273
Nephropathy	22 (12.2)	14 (6.3)	0.041
Albuminuria or proteinuria	20 (11.0)	31 (14.0)	0.231
Amputation	3 (1.7)	1 (0.5)	0.239
Stroke	5 (2.8)	3 (1.4)	0.257
Coronary artery disease	23 (12.7)	19 (8.6)	0.175
Myocardial infarction	4 (2.2)	14 (6.3)	0.038
Retinopathy	50 (27.6)	63 (28.4)	0.867

Values are presented as numbers and percentages (%).

GERD: gastroesophageal reflux disease, OHA: oral hypoglycemic agents

nephropathy ($p=0.044$) (Table 5). Whereas smoking was negatively correlated with GERD (odds ratio=0.217, $p=0.017$).

After multivariate adjustment, the only variables found to be independently associated with higher GERD prevalence were female gender ($p=0.013$) and age >65 years ($p=0.007$) (Table 6).

Discussion. We investigated GERD prevalence in patients with DM in relation with gender, age, BMI, smoking status, duration of diabetes, the different therapeutic plans such as diet, exercise, OHA, or insulin, and the presence of peripheral numbness, neuropathy, retinopathy, nephropathy, albuminuria, HTN, CAD, MI, stroke, or limb amputations.

In many countries, GERD has been reported to be more prevalent among diabetic patients than the general population.^{9,10} In China, patients with DM were found to have a prevalence of GERD that is 3 times higher compared to the general population.¹⁰ In Turkey, the estimated GERD prevalence in DM patients was 68%.¹² A meta-analysis of 9 studies from Asian and Western regions reported that DM and GERD were significantly associated. However, most of these studies were cross-sectional; thus, a causal relationship could

Table 5 - Univariate logistic regression for risk factors of GERD.

Risk factor	OR	95% CI		P-value
		Lower	Upper	
<i>Gender</i>				
Female	2.01	1.30	3.12	0.002*
Male†	1.00			
<i>Age</i>				
<45†	1.00			
45-65	1.63	0.96	2.77	0.071
>65	2.70	1.33	5.47	0.005*
<i>Body mass index</i>				
BMI <25†	1.00			
Overweight	1.81	0.96	3.43	0.067
Obese	2.19	1.21	3.95	0.009*
<i>Smoking status</i>				
Smoker	0.217	0.062	0.757	0.017*
Non-smoker or ex-smoker†	1.00			
Numbness	1.61	1.06	2.43	0.024*
Nephropathy	2.06	1.02	4.14	0.044*

*significant p -value, †used as a reference, OR: odds ratio, CI: confidence interval, GERD: gastroesophageal reflux disease

Table 6 - Multivariate logistic regression for risk factors of GERD.

Risk factors	OR	95 % CI		P-value
		Lower	Upper	
<i>Gender</i>				
Female	1.83	1.14	2.94	0.013*
Male†	1.00			
<i>Age</i>				
<45†	1.00			
45-65	1.48	0.85	2.57	0.162
>65	2.81	1.32	5.99	0.007*
<i>BMI</i>				
BMI <25†	1.00			
Overweight	1.65	0.85	3.19	0.140
Obese	1.77	0.94	3.34	0.077
<i>Smoking status</i>				
Smoker	0.30	0.08	1.10	0.070
Non-smoker or ex-smoker†	1.00			
Numbness	1.46	0.94	2.28	0.094
Nephropathy	1.50	0.71	3.17	0.285

* Significant p -value. † Used as a reference. OR - odds ratio, CI - confidence interval, BMI - body mass index.

not be determined.¹³ In this study, the prevalence of GERD among diabetic patients was 44.9%.

In the general population of KSA, GERD is associated with obesity and older age.^{8,14} The potential association between GERD and smoking among the KSA general population is controversial. One study reported no difference in the prevalence of GERD between smokers and non-smokers, whereas another study found that smoking is strongly associated with GERD.^{8,14}

In our diabetic patients, the prevalence of GERD was significantly higher among older individuals and women. Also, GERD was most frequent among non-smokers. However, it should be noted that women formed the majority of our sample, and women in KSA rarely smoke compared to men.¹³ This might explain the low percentage of smokers in the GERD group in our study.

Among diabetic patients, studies from many countries assessed upper gastrointestinal symptoms in relation with duration of DM, therapeutic plan, or different diabetic microvascular and macrovascular complications.¹⁶⁻¹⁸ A prospective study reported that lower esophageal sphincter pressure on manometry was the lowest in patients with longer duration of DM and that abdominal discomforts were more prevalent in patients with esophageal dysmotility than patients with delayed gastric emptying.¹⁶ A case-control reported higher prevalence of esophageal dysmotility in diabetic patients who have accompanying neuropathy.¹⁷ In Bangladesh, the reported prevalence of GERD among type 2 DM patients was 78.8%, with HTN being a significantly associated risk factor. On the other hand, age, gender, weight, waist circumference, and duration of DM were similar between patients with GERD and patients without GERD.¹⁸

In this study, GERD subjects were more often female, older, obese, non-smokers, and had a higher prevalence of peripheral numbness and nephropathy on univariate analysis. However, after a multivariable adjustment, GERD was found to be significantly associated with female gender and age >65 years only.

Study limitations. The subjects were recruited from a single tertiary referral hospital. Thus, our findings cannot be generalized. However, since patients were referred to our hospital from all around the KSA, our study provides an overall fair idea regarding the diabetic population of KSA. Another limitation is that patients self-reported information about their history of being diagnosed with diabetic complications. Objective measures of these complications are needed in future research. Since this study was cross-sectional, causal relationships cannot be established.

In conclusion, the prevalence of GERD among diabetic patients was 45%. That is similar to the prevalence among general population of KSA. Diabetic patients with GERD were more often female and older >65 years. None of the other tested factors (BMI, smoking status, DM duration, therapeutic plan, or

diabetic complications) were different between GERD and non-GERD subjects.

Raising awareness about the high frequency of symptomatic GERD in diabetic patients as a complication of their DM is vital ensuring that physicians proactively identify and assess these symptoms and manage them optimally.

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