

Endoscopic Assessment of Gastroesophageal Reflux Disease Severity in Type 2 Diabetic Patients

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ABSTRACT

Background: Gastroesophageal Reflux Disease (GERD) and type 2 diabetes have impacted countries' economies, healthcare systems, and patients' social life. Much modern literature discusses the prevalence of GERD in type 2 diabetes mellitus, and few studies assess the severity of GERD in type 2 diabetes mellitus.

Objective: The aim of the current work was to assess the severity of GERD in type 2 diabetic patients compared to non-diabetic patients.

Patients and Methods: This cross-sectional study included a total of 194 patients aged 18 to 65 years with GERD attending at the Gastrointestinal Endoscopy Unit, Internal Medicine Department, Zagazig University Hospitals. All patients were diagnosed with GERD by endoscopy and were presented with esophageal and non-esophageal manifestations. Patients were divided into two groups; **Diabetic Group** included 87 patients with type 2 diabetes, and **Group 2 (control)** included 107 nondiabetic patients served as control.

Results: Typical GERD symptoms were 37.6% of cases with highly statistically significant differences between the two groups (P-value = 0.000). Heartburn was a common symptom in diabetic patients (47%), with a highly statistically significant difference between the two groups. Epigastric pain (30%) was most common in non-diabetic patients. The most common extra-esophageal manifestations in type 2 diabetic patients were hoarseness (15%) and chest pain (13%). In contrast, dysphagia (13%) was common in non-diabetics. The GERD severity was mild grade (grade A, 80%), with a statistically significant difference between the two groups. However, comparing other grades between the two groups showed significantly more severe in the type 2 diabetic group.

Conclusion: It could be concluded that type 2 diabetes mellitus patients tend to have more gastroesophageal reflux disease severity than non-diabetics. However, most patients of the two groups presented with mild endoscopic severity of gastroesophageal reflux disease.

Keywords: Gastroesophageal Reflux Disease, Type 2 Diabetes Mellitus, Endoscopy.

INTRODUCTION

Gastroesophageal reflux disease (GERD) is a chronic disease with high prevalence in Middle East and the North Africa ⁽¹⁾. Heartburn and regurgitation are common GERD symptoms ⁽²⁾. Also, GERD has extra-esophageal manifestations ⁽²⁾. Endoscopy is a tool for diagnosing GERD, and the Los Angeles classification is used to determine the severity of GERD ⁽³⁾.

There are numerous complications associated with GERD. The most well-known consequence is Barrett's esophagus, a precancerous lesion that develops into esophageal adenocarcinoma ⁽⁴⁾.

Diabetes mellitus type 2 (T2DM) is a progressive metabolic condition. Diabetes has the highest relative prevalence across the Middle East and North Africa. It has various gastrointestinal problems, and GERD is the most prevalent ⁽⁵⁾.

GERD and type 2 diabetes significantly negatively impact national economies, healthcare systems, and patients' social lives ⁽⁶⁾. The prevalence of GERD in type 2 diabetes mellitus is well discussed in modern literature. However, little research assesses GERD's severity in T2DM.

This study was aimed to assess the severity of GERD in patients with T2DM.

PATIENTS AND METHODS

This cross-sectional study included a total of 194

patients aged 18 to 65 years diagnosed with gastroesophageal reflux disease attending at the Gastrointestinal Endoscopy Unit, Internal Medicine Department, Zagazig University Hospitals.

The included 194 GERD patients were divided into two groups; **Group 1 (Diabetic)** included 87 patients with type 2 diabetes, and **Group 2 (control)** included 107 non-diabetic patients served as control.

Inclusion criteria: All patients who were diagnosed with GERD by endoscopy and were presented with esophageal and extra-esophageal manifestations.

Exclusion criteria:

- Acute metabolic complications of DM (diabetic ketoacidosis (DKA) or hyperglycemic hyperosmolar non-ketonic state (HONKS)).
- GIT condition: Barrett's esophagus. Esophageal adenocarcinoma and other malignant or benign gastrointestinal tumors. Achalasia and esophageal strictures. Active peptic ulcers of the gastroduodenal zone, and Zollinger-Ellison syndrome.
- Absolute and relative contraindications to endoscopy. Absolute contraindication to elective upper GI endoscopy is a lack of informed consent from a mentally competent patient. Relative contraindications are organ perforations and states of cardiac or respiratory decompensation.
- Alcohol abuse.

- Pregnancy and lactation in women.

Pre endoscopy:

Standard laboratory tests, overnight fasting, and informed consent were performed on all patients. On the day of the treatment, an intravenous (IV) line was placed, and a complete medical history was taken.

- History of GERD symptoms (heartburn, regurgitation, and epigastric pain).
- History of extra-esophageal manifestations of GERD (chest pain, globus sensation, dysphagia, odynophagia, asthma, laryngitis, hoarseness, chronic cough, dental erosions, pharyngitis, sinusitis, recurrent otitis media, pulmonary fibrosis).
- History of diabetes mellitus type 2 and duration of diabetes.
- History of diabetic complications (diabetic kidney disease, retinopathy, lower extremity amputation, peripheral neuropathy, cardiovascular disease, and hypertension).
- Drugs history of insulin, Sulfonylurea, Metformin, GLP-1, a thiazolidinedione, and DPP-4 inhibitor.
- History of smoking, alcohol consumption, and drug addiction.

Upper gastrointestinal endoscopy (EGD)

EGD was performed under anesthesia or sedation. Expert endoscopists performed the procedures using a gastroscope (Olympus CLV-190). They identified erosive esophagitis and assigned a Los Angeles classification to the disease's severity (LA: Grades A, B, C, and D).

Grade A mucosal fractures that are 5 mm or less in length and do not reach between the tops of two mucosal folds ⁽⁷⁾.

Grade B more than five-millimeter-long mucosal breaks that did not reach between the tops of two mucosal folds ⁽⁷⁾.

Grade C was one (or more) mucosal breaks that ran between the tops of two or more mucosal folds but covered less than 75% of the circumference ⁽⁷⁾.

Grade D was one or more mucosal breaks involving at least 75% of the esophageal circumference ⁽⁷⁾.

After completing the procedure, the patient made kept for observation. After full recovery, the patient was discharged.

Ethical Consideration:

This study was ethically approved by Zagazig University's Research Ethics Committee (ZU- IRB #9375-9-3-2022). Written informed consent of all the participants was obtained. The study protocol conformed to the Helsinki Declaration, the ethical norm of the World Medical Association for human testing.

Statistical analysis

The Statistical Package for Social Science (IBM SPSS) version 20 was used to collect, edit, code, and input the data. When the distribution of the quantitative data was parametric, we displayed the quantitative data as mean, standard deviations, and ranges while we showed the qualitative data as numbers and percentages. When the predicted count in any cell was less than 5, the comparison between the two groups was done using the Fisher exact test in place of the Chi-square test. Using an independent t-test, two independent groups with quantitative data and parametric distribution were compared. 95 percent of the time was set aside for the confidence interval, and 5% of the allowed margin of error. Therefore, the p-value was deemed significant as follows: P > 0.05 = non-significant (NS), P 0.05 = significant (S), and P 0.001 = highly significant (HS).

RESULTS

Among the patients in the current study, 120 cases were female, and 74 were male. The mean age was 49 ± 8 years in diabetic patients and 38 ± 13 in non-diabetic patients. There were highly statistically significant differences between the diabetic and non-diabetic groups regarding age and sex no difference (Table 1).

Table (1): Comparison between the diabetic and nondiabetic groups regarding sex and age.

Clinical Data		Diabetic	Non-diabetic	Total	Test value	P-value	Sig.
		No. = 87	No. = 107	No.= 194			
Age (year)	Mean ± SD	49.19 ± 8.16	37.90 ±13.34	43.17 ± 12.48	7.086*	<0.001	HS
	Range	25- 65	18 - 65	18–65			
Sex	Female	52 (59.8%)	68 (63.6%)	120 (61.9%)	0.291*	0.590	NS
	Male	35 (40.23%)	39 (36.4%)	74 (38.1%)			

In diabetic patients, 68% were presented with GERD symptoms (Regurgitation, Heartburn) compared to 19% of non-diabetics with highly statistically significant (P-value = 0.000) (Table 2).

Table (2): Comparison between the diabetic and the nondiabetic groups regarding the main presentation

Main Presentations		Diabetic No. = 87		Non-diabetic No. = 107		Total		Test value*	P-value	Sig.
		No.	%	No.	%	No.	%			
GERD Symptoms	Yes	59	68%	20	19%	79	40.72%	48.8455	0.000	HS
	No	28	32%	87	81%	115	59.28%			
Heartburn		41	47.1%	8	7.5%	49	25%	39.960	0.000	HS
Regurgitation		18	20.7%	12	11.2%	30	15%	3.295	0.069	NS
Epigastric pain		10	11.5%	56	52.3%	66	34%	35.659	0.000	HS
Dyspepsia		0	0.0%	9	8.4%	9	5%	7.674	0.006	HS
Other		23	26.4%	30	28.0%	53	27%	0.062	0.803	NS
Test value		63.640*				-	-	-	-	-
P-value		0.000				-	-	-	-	-
Sig.		HS				-	-	-	-	-

Only 73 cases had extra-esophageal manifestations, and 121 had no extra-esophageal manifestation. Regarding Extra-esophageal manifestation was highly statistically significant differences between the diabetic and the non-diabetic group. Hoarseness and Sleep Disturbance were the highly statistically significant difference and common in the diabetic group, and sinusitis was a significant difference in both groups and common in the diabetic group. Dysphagia also had a highly significant difference in both groups and was common in non-diabetic group (Table 3).

Table (3): Distribution of the diabetic and nondiabetic groups according to the Extra-esophageal manifestation

		Diabetic group		Non-diabetic group		Total		Test value*	P-value	Sig.
		No.	%	No.	%	No.	%			
Extra-esophageal manifestation	Yes	45	51.7%	28	26.2%	73	37.6%	13.353	0.000	HS
	No	42	48.3%	79	73.8%	121	62.4%			
Dysphagia		0	0.0%	14	13.1%	14	7.2%	12.269	0.000	HS
Chest pain		11	12.6%	7	6.5%	18	9.3%	2.122	0.145	NS
Hoarseness		13	14.9%	4	3.7%	17	8.8%	7.534	0.006	HS
Globus sensation		8	9.2%	4	3.7%	12	6.2%	2.462	0.117	NS
Chronic cough		1	1.1%	0	0.0%	1	0.5%	1.236	0.266	NS
Dental erosions		2	2.3%	0	0.0%	2	1.0%	2.485	0.115	NS
Recurrent otitis		2	2.3%	0	0.0%	2	1.0%	2.485	0.115	NS
Sleep Disturbance		6	6.9%	0	0.0%	6	1.0%	7.615	0.006	HS
Sinusitis		5	5.7%	0	0.0%	5	2.6%	6.312	0.012	S

There were highly statistically significant differences between the Diabetic and the Non-diabetic Groups regarding GERD Classifications grades A & B and statistically significant differences in grades C & D (Table 4).

Table (4): Comparison between the diabetic and the non-diabetic groups regarding endoscopic severity GERD

GERD Classifications LA	Diabetic Group (no. =87)		Non-diabetic Group (no. =107)		Total		Test value*	P-value	Sig.
	No.	%	No.	%	No.	%			
A	64	73.6%	91	85.0%	155	80%	11.073	0.000	HS
B	16	18.4%	12	11.2%	28	14%	7.396	0.006	HS
C	5	5.7%	3	2.8%	8	4%	5.987	0.014	S
D	2	2.3%	1	0.9%	3	2%	5.160	0.023	S

Table (5) shows that 49.4% were peripheral numbness, 40.2% were hypertension, 29.9% were retinopathy, and 16.1% were nephropathy.

Table (5): DM complications.

Diabetes Complications	Diabetic Group No. = 87	
	No.	%
Peripheral numbness (? neuropathy)	43	49.4%
Hypertension	35	40.2%
Nephropathy	14	16.0%
Retinopathy	26	29.9%

Table (6) shows there were 19 (21.84%) cases were metformin + DPP4, 19.54% were Insulin + metformin, 16% were metformin, 13.79% were Metformin +Sulfonylurea, 8% were Insulin +DPP4+ Metformin, 5.75% were Metformin + DPP4 + Thiazolidinedione, 5.75% were Sulfonylurea, and 2% insulin **fig (20)**.

Table (6): Diabetic Medications.

Medications	Diabetic Group No.= 87	
	No.	%
Insulin	2	2.30%
Metformin	14	16.09 %
Sulfonylurea	5	5.75%
DPP-4 inhibitor	6	6.90%
Insulin + metformin	17	19.54 %
Metformin +Sulfonylurea	12	13.79 %
Metformin + DPP4	19	21.84 %
Insulin +DPP4+ Metformin	7	8.05%
Metformin + DPP4 + Thiazolidinedione	5	5.75%

DISCUSSION

GERD and T2DM have become more common over the past two decades. The relationship between GERD and type 2 diabetes has increased healthcare costs and slowed economic development ⁽⁸⁾.

In the modern literature review, most studies concentrated on GERD's prevalence and risk factors associated with T2DM. A few studies concentrated on the severity of GERD in T2DM patients ⁽⁸⁾.

We raised the question: What is the severity of GERD in patients with T2DM? Regarding the severity of GERD in our study, we used endoscopy to assess the severity of GERD and classified the GERD according to the Los Angeles classification. Most cases were mild GERD severity (LA-A, 80% of all cases).

More severe GERD (LA-B and higher) was more in the diabetics than in the non-diabetic patients. In comparing the diabetic and non-diabetic groups, we found the LA-B was 18.4% vs. 11.2% with highly

statistically significant (**P** = 0.006), the LA-C was 5.7% vs. 2.8% with significant statistical redistribution (**P** = 0.014), and the LA-D was 2.3% vs. 0.9% with significant statistical redistribution (**P** = 0.023).

Zhelezniakova et al. ⁽⁸⁾ found that erosive esophagitis was more common in patients with GERD with T2DM and a resultant shift in the direction of the disease's severity. **Ha et al.** ⁽⁹⁾ reported that did not find an association between the two groups. While **Lorentzen et al.** ⁽¹⁰⁾ reported no statistically significant distinction between the two categories, most cases were mild.

The mild severity of GERD may be the most common because empirical proton pump inhibitors mask the endoscopic finding.

Females were more common than males in type 2 diabetics and non-diabetics in our study. Also, **Zhang et al.** ⁽¹¹⁾ GERD is more prevalent in females than males. In contrast, **Sakitani et al.** ⁽¹²⁾ and **Fujiwara et al.** ⁽¹³⁾ showed that both sexes reported more cases of endoscopic GERD in males than females.

The peak age of GERD patients in this study ranged from 42 to 53 years in both sexes. **Tidake et al.** ⁽¹⁴⁾ and **Wang et al.** ⁽¹⁵⁾ reported that most of the patients in their studies were 30-60 years old.

The current study showed a statistically significant variation between T2DM patients and non-diabetics with GERD regarding age; non-diabetic patients were younger than diabetic patients. **Sakitani et al.** ⁽¹²⁾ found that non-diabetics were younger than people with diabetes. **Ikeda et al.** ⁽¹⁶⁾ found a correlation between GERD and younger age in patients with type 2 diabetes.

More than one-third (38%) of the overall patients in this study presented with GERD symptoms (Heartburn and Regurgitation). In diabetic patients, about 68% had symptoms compared to non-diabetics, with 19% having GERD symptoms with high significance (P-value = 0.000).

Karpenko et al. ⁽¹⁷⁾ observed that GERD symptoms were more common in patients with T2DM than in the non-diabetics. Asymptomatic cases account for about a third of patients, with the other two-thirds having symptoms ranging from typical symptoms to dysphagia and dyspeptic symptoms.

Heartburn was most significant and common in diabetic patients in 47% of cases compared to 7.5% in non-diabetics in our study. **Lin et al.** ⁽¹⁸⁾ reported that heartburn is a common symptom of GERD due to many factors.

Epigastric pain is the most common symptom in non-diabetic cases, about 52% in the current study compared to 13% in diabetic patients. **Vakil et al.** ⁽²⁾ said that heartburn and regurgitation were GERD characteristics in the general population. **Durazzo, et al.** ⁽¹⁹⁾ found that the most common extra-esophageal symptom was non-cardiac chest discomfort, consistent with previous estimates that one-third of GERD

patients would report such symptoms (23 % vs. 9 % in our study). **Karpenko et al.** ⁽¹⁷⁾ stated that non-cardiac pain and laryngopharyngeal symptoms were prevalent in persons with GERD and type 2 diabetes.

Peripheral numbness was the most common diabetic complication in our study and affected about 49% of type 2 diabetic patients. It manifested peripheral neuropathy, which would occur as a diabetes complication or as a side effect of the drugs (e.g., metformin). **Altassan et al.** ⁽²⁰⁾ reported that the prevalence of peripheral numbness (69% vs. 49% in our study) and Nephropathy (12% vs. 16%) is more common in diabetic people with GERD than in patients who do not have GERD.

Syrine et al. ⁽²¹⁾ revealed that parasympathetic disruption of the autonomic nervous system was significantly correlated with GERD but not with peripheral neuropathy.

Lee et al. ⁽²²⁾ observed that the number of patients with typical GERD symptoms was similar across the two groups. However, erosive esophagitis was more common in individuals with T2DM and neuropathy than in patients who do not have neuropathy. There was a high incidence of asymptomatic erosive esophagitis in the patients with neuropathy. Even though hypertension was widespread in our sample (40%), several investigations have found it insignificant in diabetes individuals ^(20, 23).

Our study showed that 87.4% of cases took metformin, which may be one of the causes of GERD in type 2 diabetics. To the best of our knowledge, no study in the recent literature has found a link between diabetes medications and GERD.

Ha et al. ⁽⁹⁾ stated that there is no evidence linking medication use and GERD in diabetic patients.

STUDY LIMITATIONS

As the current study was a cross-sectional study; a future prospective study is required. This study did not use pH monitoring which is a gold standard approach for diagnosing GERD. All study participants came from the same hospital and shared a common racial background. This means that we cannot generalize our results.

Furthermore, the data were collected from patients without documentation verifying their diabetes diagnosis, duration of diabetes, diagnosis of complications, or prescription history. Future studies will need to take steps to resolve these challenges. The study's cross-sectional design precludes concluding cause and effect.

CONCLUSION

It could be concluded that type 2 diabetes mellitus patients tend to have more gastroesophageal reflux disease severity than non-diabetics. However, most patients of the two groups presented with mild endoscopic severity of gastroesophageal reflux disease.

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