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Original article

Diabetic Patients with Gastro-Esophageal Reflux Disease: Comparison Between Two Self-Report Questionnaires.

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Abstract:

Background: Patients with diabetes mellitus (DM) are more likely to have gastroesophageal reflux disease (GERD), and there is a significant association between the two conditions. A variety of tools, including endoscopy, pH monitoring, and proton pump inhibitor (PPI) test, are available for the diagnosis of GERD. GERD is very prevalent among the majority of people; thus it is highly appealing to apply low-cost, simple methods for identifying high-risk people who might be suffering from it. **Aim:** To assess the diagnostic usefulness of the Carlsson-Dent (CD) questionnaire and the frequency scale for detecting the symptoms of the gastroesophageal reflux disease (FSSG) questionnaire as a self-assessment diagnostic instrument in diabetic patients and its relationship with diabetes complications. **Patients and methods:** This cross-sectional study included 217 adult diabetic patients; 153 females, 64 males who were enrolled

DIABETES,
STEATOSIS
DYSLIPIDEMIA

in two Endocrinology clinics; the Cairo University hospitals and Beni-Sweif University hospitals from June 2023 to December 2023. All patients were subjected to both CD and FSSG questionnaires (CDQ & FSSGQ respectively). Relevant clinical and laboratory data were gathered such as body mass index (BMI), diabetes control, other comorbidities, added to abdominal ultrasonography. **Results:** Using the CD questionnaire, GERD was reported in 66% of the study population versus a prevalence of 53% with the FSSGQ. There was a significant agreement between the two questionnaires: of 81.6%, p <0.0001. The presence of hypertension and liver steatosis were significantly associated with GERD diagnosis by the CDQ (*P*-value 0.03 and 0.004 respectively) and FSSGQ (*P*-value 0.01 for both). Additionally, NSAID intake, as well as peripheral neuropathy, were associated with GERD using the CDQ (*P*-value 0.03 and 0.004 respectively). Dyslipidemia was associated with GERD using the FSSGQ (*P*-value 0.008). **Conclusion:** A relatively high incidence of GERD symptoms in diabetic patients was observed. There was a significant agreement between the CD and FSSG questionnaires. Hypertension, liver steatosis, dyslipidemia, peripheral neuropathy, and NSAID intake were associated with GERD in diabetics.

1. Introduction:

The chronic gastrointestinal illness known as gastroesophageal reflux disease (GERD) is defined by the reflux of contents from the stomach into the esophagus. It is one of the most common digestive illnesses, causing substantial direct and indirect cost burdens as well as a negative impact on quality of life [1].

Older age, high body mass index (BMI), smoking, anxiety, depression, and less physical activity while working are risk factors for GERD [2]. One apparent prominent factor is hypertension [3].

Furthermore, patients with diabetes not only have an increased risk of developing GERD, but they may also exhibit unusual GERD symptoms. Therefore, in order to

provide the best care possible for these patients, medical professionals treating them must be aware of the established correlations between both of these illnesses. Neuronal function and gastrointestinal motility are negatively impacted by both acute and chronic hyperglycemia, which is one of the pathophysiological alterations seen in diabetes patients. As a result, gastroparesis and esophageal dysmotility are frequent in diabetic individuals, which may precipitate the development of GERD [4,5].

In order to quickly and precisely identify patients, choose the best course of treatment, and evaluate their response to treatment without wasting a lot of resources on tests, questionnaires are vital tools. likewise they are crucial elements of clinical trials that seek to thoroughly assess medications for long-term conditions such GERD, functional dyspepsia, and irritable bowel syndrome [6].

To assess digestive symptoms, a number of questionnaires have been created and employed, including the frequency scale for the symptoms of gastroesophageal reflux disease questionnaire (FSSGQ) [7] and the Carlsson Dent (CD) surveys [8].

However, for a variety of reasons—including the complexity of the questions—no questionnaires are frequently utilized in clinical settings. Many studies have compared various questionnaires with an emphasis on their responsiveness, authenticity, and accuracy [9, 10], but less have focused on the simplicity, convenience, and clarity of questionnaires in clinical settings [11].

2. Patients and Methods:

Study population

Patients who provided informed consent were enrolled in this study that was conducted at the Endemic Medicine Department, Cairo University and Internal Medicine Department, Beni-Sweif University in collaboration with Endocrinology clinics - Cairo University hospitals and Beni-Sweif University hospitals from June 2023 to December 2023.

Inclusion criteria included adult patients with any type of DM. Patients younger than 18 years or with a history of malignancy or current malignancy or chronic illness that may cause symptoms comparable to those of GERD were excluded.

Study protocol

The protocol for the study was given approval by the Research Ethical Committee of the Faculty of Medicine, Beni-Sweif University (FMBSUREC/02012024/Matar123457).

Every participant underwent a thorough history taking that covered their age, parity, place of residence, type of employment, and any particular medically relevant habits, like smoking. Special concern about

the following: body weight, height, BMI, tobacco use, and alcohol consumption added to drug intake, especially PPI and NSAIDS.

The World Health Organization (WHO) and the American Diabetes Association (ADA) criteria were also used by the study investigator to confirm the diagnosis of DM [12, 13]. Type of diabetes. Duration of diabetes, medications for diabetes; oral hypoglycaemic drug or insulin, or both together with complications of diabetes especially peripheral neuropathy were reported. Cardiovascular troubles respiratory disorders, hepatic disorders, blood disorders, or a tendency for bleeding, and a history of previous surgery were evaluated. The study researcher carried out the diagnosis of hypertension using WHO guidelines [14].

Diagnosis of GERD by the study questionnaires

All patients underwent complete history taking, answered FSSG and CD questionnaires after translation and edition to the Arabic language and clarified for participants upon reading it [7, 8].

Physical examination was performed with emphasis on vital signs, signs of pallor, jaundice, lymph node enlargement, and proper abdominal examination. Abdominal ultrasonography was done for patients who were complaining of dyspeptic symptoms screening for gall bladder stones. None of the patients had alarming symptoms necessitating an upper endoscopy. By dividing bodyweight in kilograms by height in meters squared, the BMI was obtained.

Blood sample collection and testing

All subjects underwent morning examinations following a 10-hour to 12-hour fast, in addition to venous blood sample of 3 milliliters was obtained. In three months, the serum was used for analysis after being separated in two hours and kept at -80° C. Their clinical information and blood samples were collected. HbA1c, fasting plasma glucose and 2 hours post-prandial glucose, insulin, and serum lipids were measured.

Statistical analysis

Descriptive statistics were performed, and qualitative data was presented by number and percentage, whereas the mean, standard deviation, median, and interquartile range were used to represent quantitative data. FSSGQ and CDQ were classified as positive for the diagnosis of GERD with a score >8 or>4 respectively or negative [7, 8]. The agreement between the two questionnaires was assessed using the Kap inter-rater agreement test. Logistic regression was performed to investigate predictors of GERD diagnosis by each questionnaire. P values <0.05 were considered significant. STATA 15.1 was used for the analysis.

3. Results:

This prospective study included 217 adult diabetic patients attending the Endocrinology Clinics at Kasr Al-Ainy Medical School and Beni-Sweif University Hospitals. Their median age was 50 years (range: 18-75), and 70.5% of them were females.

The majority of individuals in this research had type II diabetes, with a median duration of seven years (3-13) and most of them had fair or poor diabetes control. Only around nineteen percent of the study population had normal body weight nevertheless the remaining individuals were either obese or overweight, **Table 1**.

Table 1. Baseline characteristics of the study population

Age	50 (40-58) Range: 18-75
Gender Male/Female	 64 (29.5%)/ 153(70.5%)
Smoking	17 (7.8%)
Type of DM	
Type I DM	32 (14.75%)
Type II DM	185 (85.25%)
Medication for DM	
Insulin	93 (42.86%)
Oral anti-diabetic	101 (46.5%)
Both	23 (10.6%)
Duration of DM (years)	7 (3-13) Range: 1-40
Other medications	
NSAIDs	52 (23.96%)
PPI	44 (20.3%)
Hypertension	94 (43.3%)
Dyslipidemia	155 (71.4%)
Liver steatosis	126 (58.1%)
BMI	31 (26-37.1) Range: 16.6-54.7
Obesity grades by BMI	
Normal	41 (18.9%)
Overweight	61 (28%)
Obese class I	49 (22.6%)
Obese class II	28 (12.9%)
Obese class III	38 (27.5%)
Laboratory tests	
HbA1C	7.5 (6.8-8.8) Range: 5.6-14.9
Triglycerides	140 (94-205) Range: 51-350
Cholesterol	173 (130-205) Range: 59-290
LDL-cholesterol	87 (69-116) Range: 37-186
HDL-cholesterol	50 (45-65) Range: 30-100

Unless otherwise specified, numerical data are presented as median (IQR)

Using the CD questionnaire, GERD was reported in as high as 66% of the study population versus a prevalence of 53% with the FSSGQ, **Figure 1**.

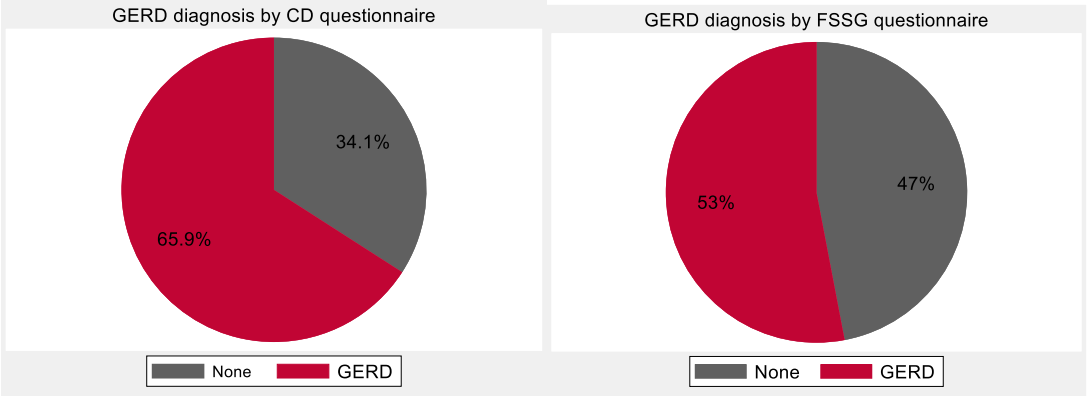

Figure 1. Diagnosis of GERD using CD and FSSG questionnaires reported in the Population of study.

Positive scores using CDQ (≥4) were compared to positive scores for the FSSGQ (>8). The agreement between the two questionnaires was assessed using the kap interrater agreement for two unique raters. It revealed a statistically significant agreement of 81.6%, *P*-value<0.0001, **Table 2**.

Table 2. The agreement between the CD and the FSSG questionnaires

Agreement	**Expected agreement**	**Kappa (SE)**	**P**
81.57%	51%	0.6 (0.1)	**<0.0001**

Predictors of GERD diagnosis with each questionnaire were studied and presented in **Table3**. Neither the type of DM, its duration nor diabetes control significantly predicted GERD diagnosis. Liver steatosis and hypertension were found to be significantly related with higher odds of GERD diagnosis by the two questionnaires. Additionally, NSAID intake as well as peripheral neuropathy were associated with higher odds of GERD using the CDQ. Also, dyslipidemia was associated with higher odds of GERD using the FSSGQ.

Table 3. Predictors of GERD diagnosis with the study questionnaires

	CD questionnaire (≥ 4)		**FSSG questionnaire (>8)**	
	OR (95% CI)	***P***	**OR (95% CI)**	***P***
Age	0.98 (0.96-1.01)	0.2	0.98 (0.96-1.01)	0.2
Gender Female	0.68 (0.36-1.28)	0.2	0.99 (0.55-1.78)	0.9
Duration of DM	0.99 (0.96-1.03)	0.6	1.01 (0.98-1.04)	0.6
HBA1C	1.09 (0.91-1.30)	0.3	1.06 (0.90-1.25)	0.5
Type of DM	0.6 (0.26-1.41)	0.2	0.74 (0.34-1.58)	0.4
BMI	1.03 (0.99-1.07)	0.1	1.03 (0.99-1.1)	0.08
Hypertension	2.23 (1.1-4.54)	**0.03**	2.42 (1.24-4.72)	**0.01**
NSAID intake	2.30 (1.10-4.81)	**0.03**	1.58 (0.84-2.99)	0.2
Neuropathy	2.02 (1.02-4.01)	**0.04**	1.88 (0.98-3.61)	0.06
Dyslipidemia	1.77 (0.97-3.26)	0.06	2.25 (1.23-4.11)	**0.008**
Liver steatosis	2.31 (1.30-4.1)	**0.004**	2.03 (1.17- 3.50)	**0.01**

4. Discussion:

Globally, the number of cases of GERD is rising. GERD is characterized by a chronic reflux of the contents of the stomach into the esophagus, oral cavity, or lungs [15].

GERD is among the gastrointestinal illnesses for which diabetes is a major risk factor. But other illnesses like neuropathy, infections, and neoplasia can also be related to this disease [16].

Approved screening measures are required for each group to identify individuals who may benefit from further testing such as esophagogastroduodenoscopy, given that a thorough workup for GERD is expensive, time-consuming, and occasionally ineffective. Clinical GERD scales are extensively used and have been verified in a variety of settings, including individuals with DM. On the other hand, not much is known about how these tools are used in Egyptian patients with DM [17].

The present study sought to assess the prevalence of GERD symptoms using the

FSSG and CD questionnaires in order to determine the frequency of GERD in diabetic patients and compare the results of two questionnaires to each other. To obtain this aim, 217 diabetic patients were randomly enrolled.

The median age in this study patients was 50 years ranging between 18 and 75 years. In AlTassan et al., (2020) study, the mean age of GERD patients was 55.27 years. Moreover, the mean age of GERD patients was 44.1 ± 12.0 years in the Quach & Phan., (2022) study. Previous studies revealed that the frequency of GERD increased with the increase in age [18, 19].

The prevalence of GERD differs among nations and ethnic backgrounds based on their food habits and other biologic and cultural variations, yet it is widespread in the population in general [20]. In the current study, 115 (53%) patients were diagnosed as GERD using FSSGQ while 140 (65.9%) patients were diagnosed as GERD using CDQ. According to AlTassan et al., (2020) study on diabetic patients in Saudi Arabia, the prevalence of GERD was 44.9% using the GERD questionnaire (GERDQ), which is near to what we observed in the present study [18]. The similarity in eating habits, rich in fatty and spicy food, between Egypt and Saudi Arabia can be the cause of similar incidences of GERD in both studies. A lower incidence of GERD was reported in Valdez-Solis et al., (2017) study from México, FSSGQ was positive in 39% of long-standing diabetes type I patients, and CDQ was positive in 28% of patients [20].

The present study reported a significant agreement between CDQ and FSSGQ in GERD diagnosis, with an agreement of 81.57% and $P<0.0001$. The results are more accurate when numerous scales are used. The CDQ has the benefit of being simple to use and approved in many demographics. It was developed by first-contact clinicians. Nevertheless, it has a somewhat sophisticated scoring system and is restricted from being applied while the patient is receiving treatment [21].

As reported by Jones & Ravich, (2013), the FSSG questionnaire was adequately correlated with endoscopic results and has the benefit of being applied to individuals who are receiving medical care [21]. Additionally, 255 GERD patients who completed the FSSGQ and had an endoscopy were investigated by Miyamoto et al. (2008). They came to the conclusion that FSSG could identify patients who would benefit from maintenance therapy [22].

On the contrary, Contreras-Omaña et al., (2017), compared the CDQ and the GQQ (GERD-DQ) questionnaire on 220 individuals from the general population, no correlation was reported between the results of the 2 questionnaires. Contreras-

Omaña et al., suggested that The GQQ could be more helpful for patients who are overweight, and the different variables assessed may have contributed to the lack of relationship between the two questionnaires [23].

GERD patients who were diagnosed using CDQ in the current study had a significantly higher incidence of NSAID intake (P=0.03). In line with our findings, Kariri et al., (2020) reported that GERD was associated with analgesic use [24]. Moreover, there was an association between NSAID consumption with GERD in Zein et al., (2022) study [25].

GERD is definitely an illness that is closely linked to obesity. GERD is twice as common in overweight people, and 50% of patients with severe obesity have GERD symptoms [26]. In Eusebi et al., (2018) meta-analysis, GERD symptoms are more common overall in obese individuals than in non-obese ones [27]. Some of the effects of obesity on GERD might be confounded by associated differences in diet or physical activity. As reported by Nocon et al., (2006) GERD has been inversely correlated with fruit and fiber consumption and positively correlated with higher intake of sugar, fatty foods, chocolate, and salt [28].

Although being obese is one of the characteristics known to induce GERD, we did not find a significant correlation between obesity and the occurrence of GERD in our research. According to Hsu et al. (2011), obesity and GERD severity and prevalence are correlated. This could be explained by the fact that the majority of participants in our sample had high BMIs (81.1% of them were overweight or obese) [29].

According to the present study, dyslipidaemia constituted a significant predictor of GERD diagnosis by the FSSGQ and a borderline significance by the CDQ. In agreement with our study, Gong et al., (2019) reported that levels of triglycerides, and cholesterol were significantly higher in the GERD group than in the non-GERD group [30]. Furthermore, Hirata et al., (2012) utilized the FSSGQ on type 2 diabetics to detect the presence of GERD and he reported that in patients with type II diabetes, dyslipidemia may have a role in the development of GERD symptoms [31].

Liver steatosis, identified by the presence of fatty liver by ultrasonography, was also a substantial indicator of GERD diagnosis by the two questionnaires. Similarly, He et al., (2022) revealed the Gastroesophageal Reflux Symptoms (GERS) group had a significantly greater prevalence of metabolic dysfunction-associated fatty liver disease than the non-GERS group [32].

Hypertension was found to be a substantial factor for GERD in our cohort when we

used both CDQ and FSSGQ (*P* was 0.03 and 0.01 respectively), this was reported also by Li et al., 2018 who found a significant correlation between hypertension and GERD as GERD can provoke high blood pressure as well. On the other side, Nandyalet al., 2017 showed that the relationship between GERD and hypertension was not statistically significant (p=0.748) [33,34].

Peripheral neuropathy constituted a distinct factor of risk for GERD when we studied our cohort using CDQ and this was in agreement with Wang et al., 2008 who found that GERD symptoms are more common in neuropathy patients than in non-neuropathic persons. (58.7% vs 32.7%, $P < 0.01$). However, this finding couldn't be confirmed when Sehe Dong Lee, et al., 2011 used Reflux Symptom Index >13 and Reflux Finding Score >7 to diagnose GERD and this elucidates the importance of using an illustrative self-reported questionnaire like CDQ [35,36].

According to the current study, no significant relation between CDQ and FSSGQ outcomes with age, gender, or BMI. As with our work, in Valdez-Solis et al. (2017) study, the groups' age, duration of DM, and BMI were comparable when analyzing patients who had and did not have symptoms who filled out one or both positive questionnaires in a stratified analysis [20]. Furthermore, age, gender, and weight did not differ in GERD patients and non-GERD patients, according to a study conducted by Rouf et al. (2017) on 137 T2D patients from Bangladesh [37]. On the contrary, AlTassan et al., (2020) reported that, using GerdQ, GERD was more common in women (p<0.001), and among older individuals [18].

In the GERD group, mean±SD age was 55. 27±11.93 years, versus 52.43 ±15.32 years in the non-GERD patients (p=0.038). Additionally, a minor difference in BMI was seen between the two groups: patients without GERD had a mean ± SD BMI of 30.20 ± 6.6, whereas those with GERD had a mean ± SD BMI of 32.04 ± 6.6 (p=0.006). It should be highlighted, nonetheless, that the majority of the study population (68.7%) in AlTassan et al.'s research was female [18].

Furthermore, Almadi et al., (2014) and Alkhathami et al., (2017) studies on the entire populace of Saudi Arabia, Obesity and advanced age are linked to GERD [38,39].

It is crucial to note that individuals with Type 1 diabetes (T1D) are seldom researched as a distinct group, particularly in adult patients who have had diabetes for an extended period of time and may have worse illnesses. Because most adult T1D patients are relatively young (about 30 years old) and present numerous problems and even limitations when they are

supposed to be living regular lives with a better quality of life, it is critical to identify T1D patients from other T2D patients. One of the possible causes of inadequate metabolic control and a low quality of life is gastro-esophageal disorders. There is no discernible relationship between the type of DM and the CDQ and FSSGQ results, according to the current investigation. In a meta-analysis by Sun et al., (2015), there is no distinction between patients with T1D and T2D in any of the articles employed for this study [20, 40].

The duration of DM was not a significant predictor of GERD diagnosis as per the present study. Similarly, AlTassan et al., (2020) observed no distinction in the duration of DM between GERD and non-GERD individuals. In addition, Rouf et al., (2017) research found no statistically significant differences in the duration of DM between participants with and without GERD. On the contrary, Boronikolos et al., (2015) study, Patients with a longer period of DM had the lowest lower esophageal sphincter pressure on manometry [18, 37, 41].

One of the primary constraints in the present study was that upper endoscopy was not done for patients to correlate upper endoscopy results with the outcome of used questionnaires. This was due to the lack of severity of GERD symptoms among the studied patients to justify upper endoscopy. Our studied patients had no dysphagia, bleeding, odynophagia, no persistent vomiting or weight loss, no severe erosive esophagitis, and no history of esophageal stricture [42].

5. Conclusion:

CD and FSSG questionnaires had a significant degree of agreement for GERD diagnosis. Hypertension, liver steatosis, dyslipidaemia, peripheral neuropathy, and NSAID intake are associated with GERD in diabetics.

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