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The effect of diabetes mellitus on clinical symptoms and esophageal injury in patients with gastroesophageal reflux disease

Wpływ cukrzycy na obraz kliniczny i endoskopowy u pacjentów z chorobą refluksową przełyku

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Introduction: In recent years attention has been paid to the increased incidence of gastroesophageal reflux disease (GERD) among patients with diabetes, however, the relationship between glycaemic control and GERD remains unclear.

Aim: The aim of the study is to assess the impact of diabetes on clinical presentation and the occurrence of inflammatory changes in the oesophagus in patients with GERD.

Material and Methods: The study comprised 77 patients with GERD diagnosed on the basis of typical clinical symptoms assessed in the frequency scale for symptoms of GERD (FSSG). To evaluate the complications, gastroscopy was performed, classifying inflammatory changes in the oesophagus based on the Los Angeles scale. The diagnosis of Barrett's oesophagus was based on the Prague classification and histological examination. Anthropometric data (including body mass index (BMI) and waist-hip ratio (WHR)) and results of routine biochemical tests (glycemia, glycated haemoglobin (HgbA1c), lipid profile, protein) were analysed.

Results: In the examined group, 27 patients had diabetes (DM), while 50 people were non-diabetic (nDM). Patients with GERD and DM were older than nDM (66.89 ± 9.44 vs 59.63 ± 15.5 years, p = 0.029), had a higher BMI (31.21 ± 4.89 vs. 26.57 ± 4.84 kg / m2, p <0.001) and WHR (0.99 ± 0.09 vs. 0.91 ± 0.07, p <0.001). In the DM group, higher level of fasting glycemia was found (6.05 (5.5-7.49) vs. 5.29 (4.86-5.64) mmol / l, p <0.001), HgbA1c (6.42 ± 0.86 vs. 5.42 ± 0.47%, p = 0.001), triglycerides (4.7 ± 1.22 vs. 5.31 ± 1.46 mmol / l, p = 0.073), while statistically lower HDL and LDL concentrations (1.3 ± 0.32 vs. 1.48 ± 0.35 mmol / l and 2.78 ± 1.02 vs. 3.38 ± 1.21 mmol / l, p = 0.03). In comparison to the nDM group, people with DM achieved a higher FSSG score (20.75 ± 7.48 vs 17.62 ± 6.49 points, p = 0.06) and more often complained of heartburn after meals (p = 0.018). In patients with DM, inflam-

Wprowadzenie: W ostatnich latach zwraca się uwagę na zwiększoną częstość występowania choroby refluksowej przełyku (ChRP) wśród chorych z cukrzycą, jednak związek pomiędzy wyrównaniem glikemii a ChRP pozostaje niejasny.

Cel: Celem pracy jest ocena wpływu cukrzycy na prezentację kliniczną i występowanie zmian zapalnych w przełyku u chorych z ChRP.

Materiał i Metodyka: Do badania włączono 77 pacjentów z ChRP rozpoznaną na podstawie typowych objawów klinicznych w oparciu o skalę częstości występowania objawów ChRP (*frequency scale for symptoms of gastroesophageal reflux disease* - FSSG). Dla oceny powikłań wykonano gastroskopię, klasyfikując zmiany zapalne w przełyku na podstawie skali Los Angeles. Rozpoznanie przełyku Barretta ustalono w oparciu o klasyfikację praską i badanie histologiczne. Anaiizie poddano dane antropometryczne (w tym indeks masy ciała (*body mass index* - BMI) i stosunek obwodu talii do obwodu bioder (*waist-hip ratio* – WHR) oraz wyniki rutynowych badań biochemicznych (glikemia, hemoglobina glikowana (HgbA1c), profil lipidów, białko całkowite)

Wyniki: W badanej grupie 27 chorych miało cukrzycę (DM), natomiast 50 osób stanowiła grupa bez cukrzycy (nDM). Pacjenci z grupy DM byli starsi niż chorzy w grupie nDM (66,89 ± 9,44 vs 59,63 ± 15,5 lat, p = 0,029), mieli wyższe BMI (31,21 ± 4,89 vs. 26,57 ± 4,84 kg/m^2; p <0,001) oraz WHR (0,99 ± 0,09 vs. 0,91 ± 0,07; p <0,001). W grupie DM stwierdzono wyższy poziom glikemii na czczo 6,05 (5,5-7,49) vs. 5,29 (4,86-5,64) mmol/l; p < 0,001), HgbA1c (6,42 ± 0,86 vs. 5,42 ± 0,47%; p = 0,001), trójglicerydów (4,7 ± 1,22 vs. 5,31 ± 1,46 mmol/l; p = 0,073), natomiast statystycznie niższe stężenie HDL oraz LDL (1,3 ± 0,32 vs. 1,48 ± 0,35mmol/l i 2,78 ± 1,02 vs. 3,38 ± 1,21 mmol/l; p = 0,03). W porównaniu do grupy nDM osoby z DM osiągnęły wyższy wynik w skali FSSG (20,75 ± 7,48 vs 17,62 ±

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matory changes in the oesophagus were significantly more frequent (59.3 vs. 34%, p=0.03).

Conclusions: Patients with GERD and concomitant diabetes more often complain of postprandial heartburn than non-diabetic ones. DM in patients with GERD predisposes to oesophageal inflammatory changes, however further studies on a larger group of patients are necessary to confirm this thesis.

6,49 punktów; p=0,06) oraz częściej skarżyły się na zgagę po posiłkach (p=0,018). U pacjentów z DM znamiennie częściej stwierdzono zmiany zapalne w przełyku (59,3 vs. 34%; p=0,03).

Wnioski: Pacjenci z ChRP oraz współistniejącą DM częściej skarżą się na poposiłkową zgagę niż chorzy bez DM. DM wśród chorych z ChRP predysponuje do zmian zapalnych przełyku, jednak dalsze badania na większej grupie pacjentów są konieczne dla potwierdzenia tej tezy.

Introduction

Diabetes mellitus (DM) is a chronic disease that compromises the functions of almost all organs and is associated with various gastrointestinal symptoms and complications that are usually attributed to neurological impairment, especially autonomic neuropathy. Heartburn, nausea or belching are widely recognized upper gastrointestinal symptoms commonly observed in patients with DM [1].

Gastroesophageal reflux disease (GERD) is a condition characterized by reflux symptoms and/or esophageal injury such as esophagitis, strictures or Barrett's esophagus (BE) resulted from an abnormal acid or bile reflux into the esophagus. The known risk factors are obesity, pregnancy, hiatal hernia, medications that relax lower esophageal sphincter (LES), and stress [2]. In previous studies, various pathophysiological factors such as insulin resistance, hyperinsulinemia, peripheral neuropathy and metabolic syndrome were suggested as the possible risk factors for the high prevalence of the typical GERD symptoms in the type 2 DM patients [3]. The recent scarce studies have highlighted that complications of GERD are more common in patients with DM; however, the link between glycemic control and GERD is still unclear [1,4-6].

According to studies based on 24-h pH monitoring, insulin-dependent diabetic patients may have a higher prevalence of asymptomatic reflux than the general population [9]. Visceral neuropathy may reduce the perception of typical gastrointestinal symptoms in DM patients [10]. This may be the reason for difficulties in determining the frequency of GERD-related disorders, such as erosive esophagitis, in a diabetic population since the diabetic subjects may not present with symptoms leading to initiation of an endoscopic evaluation [11]. On the other hand, some studies have suggested that diabetic patients may be more susceptible to acid injury and severe acute gastric inflammation since peptic ulcer disease occurs with a high prevalence in patients with DM presenting few or no dyspeptic symptoms [10].

Although 24-h pH-impedance monitoring is a gold standard to diagnose gastroesophageal reflux disease, GERD is commonly diagnosed based on the frequency of typical symptoms. However, most patients with reflux symptoms have no evidence of esophageal injury and the non-erosive GERD (NERD) may be difficult to diagnose while based on patient reported symptoms. Even typical, the reflux symptoms depend on the patient's description and might be difficult to define in various populations [7]. To overcome these difficulties, Kusano et al. developed a questionnaire, the Frequency Scale for the Symptoms of GERD (FSSG), which addresses 12 symptoms most commonly experienced by GERD patients, represented not only by heartburn and acid taste, but also by other dyspeptic symptoms, such as the sensation of excessive fullness, especially after meals [8]. FSSG has been validated to be clinically useful for the initial diagnosis of GERD and patients with FSSG scores of more than 8 have been considered positive for its diagnosis [7].

The aim of our study was to assess the influence of DM on the clinical presentation and occurrence of inflammatory lesions in the esophagus in patients with GERD.

Patients and Methods

Seventy-seven patients from the Department of Gastroenterology and Hepatology, University Hospital in Cracow, Poland, and from the Department of Internal Medicine and Gastroenterology, 5th Military Hospital in Cracow, Poland, were involved in the prospective study. The inclusion criteria comprised: age above 18 years and GERD diagnosed on the basis on the FSSG questionnaire. The exclusion criteria were: concomitant severe acute diseases (such as myocardial infarction, stroke, pulmonary embolism, cirrhosis, severe infections), malignancies, and pregnancy. The study group consisted of 27 diabetic patients (DM) and 50 non-diabetic (nDM) subjects. GERD was evaluated based on the FSSG that included 12 questions with 5 possible answers grading the frequency of each of the symptom as presented in the table I [8]. All patients were asked to complete the FSSG questionnaire, and the cutoff score at 8 points or more was considered as positive for the GERD diagnosis. Gastroscopy was performed to assess the presence and severity of the esophageal injury and erosion lesions were evaluated according to the Los Angeles esophagitis classification, graded from A to D [12]. Depending on the gastroscopy results, the patients were classified as NERD when no mucosal injury was found, Erosive Esophagitis (EE) if the typical erosions were present, and BE if biopsy results confirmed the presence of intestinal metaplasia according to the Prague classification [13].

In the patients with DM, a thorough medical history was taken. The anthropomorphic data were collected, including weight, height, abdomen and waist circumferences. The body mass index (BMI), and the waist-hip-ratio (WHR) were calculated. Routine laboratory tests were performed in all subjects. Biochemical analyses included: complete blood cells count, and blood level of fasting glucose, glycated hemoglobin (HbA1c), lipids [(total cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides (TG)], total protein and albumin. All tests were performed using standard methodology in the clinical practice.

Table I
FSSG – Frequency Scale for the Symptoms of GERD.
Skala częstości objawów ChRP.

Question		Frequency				
		Never	Occasionally	Sometimes	Often	Always
①	Do you get heartburn?	0	1	2	3	4
②	Does your stomach get bloated?	0	1	2	3	4
③	Does your stomach ever feel heavy after meals?	0	1	2	3	4
④	Do you sometimes subconsciously rub your chest with your hand?	0	1	2	3	4
⑤	Do you ever feel sick after meals?	0	1	2	3	4
⑥	Do you get heartburn after meals?	0	1	2	3	4
⑦	Do you have an unusual (e.g. burning) sensation in your throat?	0	1	2	3	4
⑧	Do you feel full while eating meals?	0	1	2	3	4
⑨	Do some things get stuck when you swallow?	0	1	2	3	4
⑩	Do you get bitter liquid (acid) coming up into your throat?	0	1	2	3	4
⑪	Do you burp a lot?	0	1	2	3	4
⑫	Do you get heartburn if you bend over?	0	1	2	3	4

Abbreviations: BE – Barrett's esophagus; BMI – body mass index; DM – diabetes mellitus; EE – erosive esophagitis; FSSG – Frequency Scale for the Symptoms of GERD; GERD – gastroesophageal reflux disease; HgbA1c – glycated hemoglobin; HDL – high-density lipoprotein; LDL – low-density lipoprotein; LES – lower esophageal sphincter, nDM – non-diabetic patients; NERD – non-erosive reflux disease; SD – standard deviation; TC – total cholesterol; TG – triglycerides; WHR – waist-hip-ratio.

Statistical analysis

Continuous variables were presented as means and standard deviation or median and interquartile range (q1-q3). The distribution of variables was tested using the Shapiro-Wilk test. The Student's t test (ANOVA more than two groups) or the Mann-Whitney U (Kruskal-Wallis more than two groups) test were used for continuous variables to assess differences between the groups. Categorical variables were reported as the number and percentages. The chi-square test was used to compare categorical variables or as appropriate. The statistical analyses were performed using SPSS 23.0 (SPSS Inc., Chicago, IL, USA). P-values <0.05 were considered as statistically significant.

Results

Characteristics of patients

Among the DM patients, there were 16 females (59.3 %) and 11 males (40.7 %), aged 47-83 years, with the mean age of 66.8 ±9.44 years. The nDM group consisted of 31 females (62 %) and 19 males (38 %), aged 24–86 years, with the mean age of 59.6±15.5 years.

Characteristics of the studied groups and the laboratory test results are presented in table II.

The patients with GERD and DM were significantly older as compared to the nDM (66.89 ± 9.44 vs. 59.63 ± 15.5 years, p = 0.029). In the both DM and nDM groups, most subjects were females (59.3% and 62%, respectively). The diabetic patients were more obese (BMI 31.21 ± 4.89 vs. 26.57 ± 4.84 kg/m^2, p < 0.001) and demonstrated a higher level of fasting glycemia, HgbA1c, total protein and triglycerides, but the significantly lower level of LDL and HDL than in the nDM group as presented in table II. No differences were observed in total cholesterol and albumin levels in the both studied groups (Tab. II).

Esophageal injury

The comparison of the frequency of the esophageal injury in the studied groups is presented in table III.

The esophageal erosions significantly more commonly occurred in the patients with GERD and DM. As many as 51.8% of the DM subjects presented with esophageal erosions as compared to 26% of the patients in the nDM group (p=0.03).

Analysis of the responses to questions of the FSSG

The average FSSG score in the patients with GERD and diabetes was higher than in nDM GERD group, but the difference was not statistically significant (20.75 ± 7.48 vs. 17.62 ± 6.49 points, p = 0.06). The distribution of responses to the FSSG in the DM and nDM patients is presented in table IV.

The comparison of the response distribution in patients with esophageal injury ss including EE and BE, and without esophageal injury (NERD) is presented in table V.

The frequency of the responses to questions did not demonstrate statistical significance both in the DM and nDM groups and in the NERD and EE + BE subjects. The only difference was that a significantly higher number of the DM subjects suffered from heartburn after meals as compared to the nDM patients (p=0.018). No significant differences were found in responses to the remaining questions.

Discussion

Our study showed that patients with GERD and concomitant DM suffer more frequently from postprandial heartburn and are at higher risk of developing esophageal injury. Numerous reports have been published in recent years that prove the association between intensity of GERD symptoms and abdominal obesity; the latter is also believed to be a risk factor in BE

Table II
Characteristics of the studied groups and the laboratory test results.
Charakterystyka badanych grup i wyniki badań laboratoryjnych.

		DM (n = 27)	nDM (n = 50)	p-value (DM-nDM)
Age (years)	mean ± SD	66.89 ± 9.44	59.63 ± 15.5	**0.029**
Sex	F	16 (59.3 %)	31 (62 %)	0.81
BMI [kg/m^2]	mean ± SD	31.21 ± 4.89	26.57 ± 4.84	**<0.001**
WHR	mean ± SD	0.99 ± 0.09	0.91 ± 0.07	**<0.001**
Fasting glucose	median (q1-q3)	6.05 (5.5-7.49)	5.29 (4.86-5.64)	**<0.001**
HgbA1c (%)	mean ± SD	6.42 ± 0.86	5.42 ± 0.47	**0.001**
TC (mmol/l)	mean ± SD	4.7 ± 1.22	5.31 ± 1.46	0.073
HDL (mmol/l)	mean ± SD	1.3 ± 0.32	1.48 ± 0.35	**0.03**
LDL (mmol/l)	mean ± SD	2.78 ± 1.02	3.38 ± 1.21	**0.03**
TG (mg/dl)	median (q1-q3)	128 (92-165)	95 (70-129)	**0.007**
Total protein level (g/l)	median (q1-q3)	72 (67.7-74.7)	69.2 (66.1-71)	**0.04**
Albumin level (g/l)	median (q1-q3)	43.9 (42.2-46.4)	44 (41.7-45.4)	0.59
FSSG score	mean ± SD	20.75 ± 7.48	17.62 ± 6.49	0.06

Abbreviations: BMI – body mass index, DM – diabetic patients, FSSG – frequency scale for symptoms of GERD, HDL– high-density lipoprotein, HgbA1c – glycated hemoglobin, LDL – low-density lipoprotein, nDM – non-diabetic patients, TC – total cholesterol, TG – triglycerides, WHR – waist-hip-ratio.

Table III
Frequency of the esophageal injury in the studied groups.
Częstość zmian zapalnych w przełyku w badanych grupach.

	NERD	EE (A)	EE (B-D)	BE
DM	11 (40.7%)	11 (40.7%)	3 (11.1%)	2 (7.4%)
nDM	33 (66%)	7 (14%)	6 (12%)	4 (8%)

Abbreviations: BE – Barrett's esophagus, DM – diabetic patients, EE (A) – erosive esophagitis grade A, EE (B-D) – erosive esophagitis grade B – D, nDM – non-diabetic patients, NERD – non-erosive reflux disease.

Table IV
The distribution of responses to the FSSG in the DM and nDM patients.
Rozkład odpowiedzi na pytania w skali FSSG wśród pacjentów z DM oraz nDM.

Question	DM					nDM					P-value
1.	0	1	2	3	4	0	1	2	3	4	0.98
	6.9%	20.7%	24.1%	37.9%	10.3%	18%	16%	36%	28%	2%	
2.	0	1	2	3	4	0	1	2	3	4	0.17
	20.7%	0%	17.2%	51.7%	10.3%	14%	10%	26%	48%	2%	
3.	0	1	2	3	4	0	1	2	3	4	0.13
	6.9%	17.2%	24.1%	41.4%	10.3%	20%	8%	36%	34%	2%	
4.	0	1	2	3	4	0	1	2	3	4	0.12
	48.3%	13.8%	17.2%	20.7%	0%	60%	12%	24%	4%	0%	
5.	0	1	2	3	4	0	1	2	3	4	0.2
	24.1%	20.7%	27.6%	27.6%	0%	36%	18%	36%	10%	0%	
6.	0	1	2	3	4	0	1	2	3	4	**0.018**
	44.8%	13.8%	13.8%	24.1%	3.4%	34%	14%	44%	8%	0%	
7.	0	1	2	3	4	0	1	2	3	4	0.49
	13.8%	20.7%	41.4%	17.2%	6.9%	28%	14%	38%	18%	2%	
8.	0	1	2	3	4	0	1	2	3	4	0.11
	31%	17.2%	17.2%	17.2%	17.2%	30%	12%	30%	26%	2%	
9.	0	1	2	3	4	0	1	2	3	4	0.13
	62.1%	17.2%	3.4%	17.2%	0%	54%	16%	18%	6%	6%	
10.	0	1	2	3	4	0	1	2	3	4	0.56
	10.3%	24.1%	44.8%	20.7%	0%	22%	16%	38%	20%	4%	
11.	0	1	2	3	4	0	1	2	3	4	0.98
	10.3%	24.1%	27.6%	34.5%	3.4%	14%	28%	26%	30%	2%	
12.	0	1	2	3	4	0	1	2	3	4	0.14
	24.1%	13.8%	27.6%	27.6%	6.9%	46%	14%	18%	22%	0%	

Abbreviations: DM – diabetic patients, FSSG – frequency scale for symptoms of GERD, nDM – non-diabetic patients.

Table V
The distribution of responses to the FSSG in the NERD group and EE + BE group.
Rozkład odpowiedzi na pytania w skali FSSG wśród chorych z NERD i w grupie EE + BE.

Question	NERD					EE + BE					P-value
1.	0	1	2	3	4	0	1	2	3	4	0.76
	11.4%	15.9%	34.1%	36.4%	2.3%	18.2%	18.2%	30.3%	27.3%	6.1%	
2.	0	1	2	3	4	0	1	2	3	4	0.45
	18.2%	6.8%	18.2%	47.7%	9.1%	15.2%	6.1%	27.3%	51.5%	0%	
3.	0	1	2	3	4	0	1	2	3	4	0.23
	13.6%	4.5%	38.6%	38.6%	4.5%	18.2%	18.2%	21.2%	36.4%	6.1%	
4.	0	1	2	3	4	0	1	2	3	4	0.13
	54.5%	15.9%	25%	4.5%	0%	60.6%	9.1%	12.1%	18.2%	0%	
5.	0	1	2	3	4	0	1	2	3	4	0.9
	31.8%	20.5%	29.5%	18.2%	0%	33.3%	18.2%	36.4%	12.1%	0%	
6.	0	1	2	3	4	0	1	2	3	4	0.73
	31.8%	13.6%	34.1%	18.2%	2.3%	42.4%	15.2%	33.3%	9.1%	0%	
7.	0	1	2	3	4	0	1	2	3	4	0.77
	22.7%	15.9%	34.1%	22.7%	4.5%	24.2%	15.2%	45.5%	12.1%	3%	
8.	0	1	2	3	4	0	1	2	3	4	0.46
	22.7%	13.6%	29.5%	27.3%	6.8%	39.4%	15.2%	21.2%	15.2%	9.1%	
9.	0	1	2	3	4	0	1	2	3	4	0.59
	52.3%	15.9%	13.6%	11.4%	6.8%	63.6%	18.2%	12.1%	6.1%	0%	
10.	0	1	2	3	4	0	1	2	3	4	0.64
	15.9%	15.9%	38.6%	25%	4.5%	21.2%	21.2%	42.4%	15.2%	0%	
11.	0	1	2	3	4	0	1	2	3	4	0.14
	11.4%	18.2%	34.1%	36.4%	0%	15.2%	33.3%	18.2%	27.3%	6.1%	
12.	0	1	2	3	4	0	1	2	3	4	0.76
	36.4%	15.9%	15.9%	29.5%	2.3%	42.4%	12.1%	24.2%	18.2%	3%	

Abbreviations: BE – Barrett's esophagus, EE – erosive esophagitis, FSSG – frequency scale for symptoms of GERD, NERD – non-erosive reflux disease.

and nodular esophageal carcinoma development [14-23]. Additionally, publications report that complications of GERD are associated with arterial hypertension, insulin resistance and lipid disorders [7,24]. Some authors suggest that the symptoms and complications of GERD are more common in patients with DM 2 as compared to subjects without glycemia disturbances [1,4-6]. In the study performed in 2008, patients with long-term DM 2, obesity and high HgbA1c levels more commonly demonstrated the symptoms of gastrointestinal reflux as compared to the controls [25]. In turn, Rubenstein et al. [23] showed that in the population of patients with DM 2, esophagitis was more common than in non-DM subjects, while the serum insulin levels positively correlated with BE prevalence also among patients without glycemia disorders. The same authors demonstrated a positive correlation between increased levels of ghrelin and leptin, obesity-associated hormones, and the prevalence of BE in patients with GERD symptoms [23]. Thus, intensity of reflux symptoms in patients with DM 2 may also be associated with a fully-developed metabolic syndrome [26]. Visceral adipose tissue is a precursor of increased lipolysis and free fatty acids levels, leading to insulin resistance, a primary factor in the mechanisms of metabolic syndrome [7,27-29]. Visceral adipose tissue is also metabolically active and strongly associated with elevated serum levels of proinflammatory adipokines, which may play a role in the development of GERD [29]. These humoral mediators released by visceral fat tissue might alter the lower esophageal sphincter pressure or affect esophageal clearance [7].

On the other hand, Sun et al. did not demonstrate that BMI, WHR, lipid profile, arterial hypertension and insulin therapy affected the prevalence of GERD in patients with DM [3]. Similarly, tobacco smoking, alcohol consumption and diabetes in family history showed no significant effect on GERD occurrence [3]. In a large population study including 65,333 patients, a positive correlation was demonstrated between ischemic heart disease, myocardial infarct and cerebral stroke, and GERD presence, yet no correlation was noted for DM [30]. Fujiwara et al. (2015) observed that patients with DM and GERD were younger, had shorter duration of DM and showed no difference in BMI [1]. There was no significant association between the presence of concurrent GERD and diabetic complications, including peripheral neuropathy [1]. As presented above, the results of the previously reported studies are contradictory; thus, further investigations are needed to explain the association between carbohydrate and lipid metabolism and functioning of the upper gastrointestinal tract.

In the present study, we demonstrated that patients presenting with symptoms of GERD and DM were more obese as compared to the controls. The diabetic patients showed significantly higher level of fasting glycemia, HgbA1c, triglycerides, higher total protein value and lover HDL level when compared to the patients with GERD, but without DM. Interestingly, the DM patients demonstrated a significantly lower LDL cholesterol level. Similar results were observed by Domaradzki et al. in patients hospitalized due to pulmonary embolism episode - patients with DM had a better lipid profile as compared to nDM ones [31]. One might only speculate on the effect of LDL cholesterol-reducing medications (e.g. statins) that are more often taken by obese patients upon the symptoms of GERD, but nevertheless, further analyses are necessary to explain the phenomenon. Horikawa et al. demonstrated that patients with DM presenting with symptoms of GERD were more rarely administered calcium channel blockers, thiazolidinediones and antiplatelet drugs [32]. The use of insulin or oral anti-diabetes agents did not affect the occurrence of GERD [32]. On the other hand, the authors of another report demonstrated that in patients with DM and GERD, treatment with proton-pump inhibitors more often ended in a failure [33]. In the analysis carried out in 2018 and including more than twelve thousand subjects, Smith et al. observed symptoms of GERD and esophagitis more frequent in patients on statins [34].

The DM subjects achieved higher average scores in the FSSG scale, that suggests a higher intensity of reflux symptoms in this group. However, no significant differences were demonstrated in the response distribution of most of questions. Only post-prandial heartburn occurred more frequent in the DM as compared to the nDM patients. Quite contradictory results were achieved by Holub et al, who showed that DM patients less often complained of heartburn; however, the authors did not use validated forms for assessing GERD symptoms [11]. Nishida et al, investigated patients with DM 2; to evaluate the intensity of GERD symptoms, the authors employed the QUEST questionnaire and concluded that reflux symptoms were more common in the DM 2 group [35]. In this study, the prevalence of symptoms increased with an increasing duration of DM, the presence of complications (such as nephropathy, neuropathy, retinopathy) and when oral anti-diabetes medications were employed [35]. Additionally, Natalini et al. demonstrated that the mean duration of diabetes was longer by 2.5 years in patients with concomitant symptomatic GERD [36]. With the increasing duration of DM, the response to anti-reflux treatment with proton pump inhibitors deteriorated [30]. However, the authors of the above-cited studies did not perform endoscopic evaluation thus asymptomatic GERD related esophageal injury could not have been assessed [35]. Examination of the upper gastrointestinal tract in patients with DM is significant, since GERD was demonstrated to show a high prevalence in asymptomatic patients with abnormalities of carbohydrate metabolism [9-11]. With an increasing DM duration, complications develop increasingly more commonly, such as neuropathy of the motor, sensory and autonomic nerves, retinopathy or nephropathy. Esophageal dysfunction in patients with DM is caused largely by autonomic neuropathy, especially the vagal nerve damage [37]. As DM duration increases, esophageal motor function deteriorates, what predisposes the subject to develop GERD [37]. It was suggested that increased abnormal gastroesophageal acid reflux in patients with DM was caused by impaired acid clearance and impairment of effective esophageal peristalsis which is related to diabetic neuropathy [25,33,37,38].

Based on endoscopy results we demonstrated that esophageal erosion lesions were more frequently present in the DM patients as compared to the nDM subjects. A higher percentage of NERD was observed in the nDM group. However, there was no difference in the frequency of BE. Similar results, i.e. a higher prevalence of esophagitis, was observed in the previous studies [11]. The results suggest that DM predisposes patients with GERD to develop inflammatory lesions in the esophagus.

Diabetes and insulin resistance are among the risk factors of carcinoma development [4,39]. Insulin may act directly on tumor cells as a mitogen, and indirectly by promoting tumor growth via aberrations in the insulin-like growth factor axis [6,39,40]. In addition, chronic inflammatory state plays a significant role in BE etiology, with BE being a precancerous state predisposing the patient to develop esophageal adenocarcinoma [27,29]. Evidence suggests that chronic inflammation triggered by GERD not only predisposes to developing BE, but that the ensuing proinflammatory state and oxidative stress have roles in malignant transformation [29]. In the study of Koppert et al. [41], patients with esophageal carcinoma more frequently presented with DM as opposed to subjects with esophageal squamous cell carcinoma. In a large population-based case-control study, DM 2 was a risk factor for BE, independent of obesity and other risk factors (e.g. smoking) [4]. The above results contradict the findings of Rubenstein et al. [42], where no correlation was proven between the occurrence of DM and esophageal adenocarcinoma. Our data demonstrate a more frequent occurrence of esophageal injury in patients with DM, but in view of the small number of the investigated subjects, further analyses are necessary.

Summing up, the present study is among the few reports in which the diagnosis of GERD was established based on the noninvasive and validated symptoms scale. Moreover, in all the patients gastroscopy was performed, that allowed us to detailed evaluation of the esophageal mucosa and possible GERD complications.

The study also has several limitations. One of them, as mentioned above is a small sample of patients. No evaluation was also performed for the effect of medications and duration of DM that might have affected the presented symptoms.

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