Erosive esophagitis and symptoms of gastroesophageal reflux disease in patients with morbid obesity with and without type 2 diabetes. A cross sectional study.

Background:

Type 2 diabetes (T2DM) is associated with gastroesophageal reflux disease (GERD) in the general population, but the relationship between these conditions in candidates for bariatric surgery is uncertain. We compared the prevalence of GERD and the association between GERD-symptoms and esophagitis among bariatric candidates with and without T2DM.

Methods: Cross sectional study of baseline data from the Oseberg study in Norway. Both groups underwent gastroduodenoscopy and completed validated questionnaires: Gastrointestinal Symptom Rating Scale and Gastro Esophageal Reflux Disease Questionnaire. Participants with T2DM underwent 24-hour pH-metry.

Results: A total of 124 patients with T2DM, 81 women, mean (SD) age 48.6 (9.4) years and BMI 42.3 (5.5) kg/m^2, and 64 patients without T2DM, 46 women, age 43.0 (11.0) years and BMI 43.0 (5.0) kg/m^2, were included. The proportions of patients reporting GERD-symptoms were low (< 29%) and did not differ significantly between groups, while the proportions of patients with esophagitis were high both in the T2DM and non-T2DM group, 58% vs 47%, p=0.16. The majority of patients with esophagitis did not have GERD-symptoms (68%-80%). Further, 55% of the patients with T2DM had pathologic acid reflux. Among these, 71% also had erosive esophagitis, whereof 67% were asymptomatic.

Conclusions: The prevalence of GERD was similar in bariatric patients with or without T2DM, and the proportion of patients with asymptomatic GERD was high independent of the presence or absence of T2DM. Accordingly, GERD may be underdiagnosed in patients not undergoing a preoperative endoscopy or acid reflux assessment.

Trial registration: Clinical Trials.gov number NCT01778738.

Keywords

Gastroesophageal Reflux Disease (GERD). Erosive esophagitis. Heartburn. Acid regurgitation. Acid reflux. Type 2 diabetes mellitus. Obesity. Bariatric surgery.

Introduction

Gastroesophageal reflux disease (GERD) is common with a worldwide prevalence of 8-33% (1-4) and GERD symptoms have been reported in up to 73% of bariatric surgery candidates (5, 6). GERD develops when the reflux of acid gastric content causes troublesome symptoms and/or mucosal damage (7) and is associated with increased risk of esophageal strictures, Barrett's esophagus and esophageal adenocarcinoma (8).

Obesity is an independent risk factor for GERD (9), partly due to obesity related hiatal hernia (10, 11), decreased lower esophageal sphincter (LES) resting pressure (9), and higher intragastric pressure (10, 12). Type 2 diabetes mellitus (T2DM) is associated with GERD independent of body weight (2, 13).

Patients with T2DM may be more susceptible to both GERD symptoms and asymptomatic erosive esophagitis (14, 15). However, whether patients with T2DM scheduled for bariatric surgery have a higher prevalence of GERD than those without T2DM is uncertain. Further, it is well known that GERD symptoms and endoscopic findings are weakly correlated (16-19), but the relationship between esophagitis and GERD symptoms in patients with or without T2DM has not been well investigated (10, 20). In addition, few previous studies have assessed the association between esophageal acid exposure and reflux symptoms or erosive esophagitis in subjects with severe obesity (10, 21, 22).

We aimed, first, to compare the prevalence of GERD symptoms and erosive esophagitis among patients with or without T2DM scheduled for bariatric surgery, hypothesizing a higher prevalence of GERD among patients with T2DM. Second, to assess whether erosive esophagitis was associated with GERD symptoms within both groups, and, third, to assess the associations between pathologic acid reflux, erosive esophagitis and GERD symptoms in patients with T2DM.

Materials and Methods

Trial design

This is a cross sectional analysis of baseline data on GERD from the Oseberg study, an ongoing, randomized, triple-blind, single-center trial, which primarily aims to assess the effects of gastric bypass and sleeve gastrectomy on remission of T2DM (23, 24).
During the first year of this study, the prevalence of erosive esophagitis was higher than expected, and the potential impact of T2DM on these findings was unclear. Therefore, to explore whether the prevalence of GERD was particularly high among patients with T2DM, the steering committee decided, in 2014, to add a control group of bariatric patients without T2DM (23).

Settings

The study was conducted at the Morbid Obesity Centre at Vestfold Hospital Trust, a tertiary care obesity center in Southern Norway between January 2013 and February 2018.

Participants

All patients scheduled for bariatric surgery at the center were screened for study eligibility. The inclusion criteria for both groups were age ≥18 years, and BMI ≥ 35 kg/m², or BMI ≥33 kg/m² with previously verified BMI≥35 kg/m².

T2DM was diagnosed in those with an HbA1c ≥ 6.5 % (48 mmol/mol) or use of anti-diabetic medications. Exclusion criteria were previous major abdominal surgery, chronic medical conditions associated with increased risk of peri- and postoperative complications, drug or alcohol addiction, mental and psychiatric conditions leading to reduced compliance, pregnancy, and previously known severe gastro-esophageal reflux disease (Los Angeles classification grade C or D, or Barrett's esophagus).

Outcomes

Prespecified secondary outcomes of the Oseberg study and the main outcomes of this analysis were GERD symptoms, erosive esophagitis and pathologic acid reflux.

GERD symptom questionnaires

The Gastroesophageal Reflux Disease Questionnaire (GerdQ) (25) is a validated 6-item questionnaire for reflux disease and includes four positive predictors for GERD; heartburn, regurgitation, sleep disturbances due to heartburn or reflux, and the use of over the counter medication, and two negative predictors for GERD; epigastric pain and nausea. The range of the total score for all six items is between 0-18. A validated Norwegian version of the questionnaire (26) was used. GerdQ was defined as positive when the score was ≥ 8 points.

The Gastrointestinal Symptom Rating Scale (GSRS) is a 15-item scale that assesses common symptoms of gastrointestinal disorders (27, 28). The GSRS – Reflux subscale includes two items; heartburn and acid regurgitation. Each item is scored from zero to six, where higher scores indicate greater severity of symptoms. The GSRS in European patient populations has a good internal consistency and reliability and acceptable construct validity and responsiveness (27, 28). The sum score was converted to a 0-100 scale to be comparable with other quality of life scales. GSRS-Reflux was defined as positive when the score was ≥20 points.

Erosive esophagitis

Esophagogastroduodenoscopy (EGD) was performed by experienced endoscopists using Olympus® 180 or190 gastroscope. Anti-reflux medication was discontinued 7 days prior to EGD. Erosive esophagitis was graded according to the Los Angeles (LA) classification (29, 30) by two experienced endoscopists who were unaware of surgical procedure, based on the image of the lower esophageal sphincter (LES). In case of disagreement, the first author and the endoscopists reviewed the case together and reached an agreement. Hiatal hernia was

measured longitudinally in centimeters from the LES to the diaphragmatic impression, and was defined as hiatal hernia if ≥ 2 cm.

A diagnosis of Barrett's esophagus or adenocarcinoma was verified in biopsies. Non-erosive reflux disease (NERD) was defined as the presence of typical symptoms of GERD in the absence of visible esophageal mucosal injury on EGD and the presence of pathologic acid reflux (31).

Ambulatory 24-hour pH-metry

Ambulatory pH-metry was performed after six hours fasting, and 7 days off proton pump inhibitor and H2 blocker, using the Digitrapper™ pH-Z Testing System, Medtronic, Minneapolis, USA.

The probe was introduced transnasally and placed 5 cm above LES after verification with high resolution manometry. Patients were asked to follow their normal daily habits, including eating habits, record upper GI symptoms, meals, medication, and supine position (bed time only). The data were recorded by a portable digital data logger for 24 hours, and DeMeester score was calculated using a standard software program (16). Pathologic acid reflux was diagnosed as DeMeester score ≥14.72 (32) or distal esophageal acid exposure time (AET) ≥ 6% (11, 16). The examination with 24 hour pH-metry was preplanned and performed only in patients with T2DM.

Sample size

A total of 120 subjects with T2DM were planned to be included in the Oseberg study (23). To show a mean (SD) clinically meaningful difference of at least 10 (20) GSRS-score points between groups with or without T2DM (power 80% and alpha 0.05), at least 44 patients without T2DM had to be included. Taking into account possible loss to follow-up and incomplete data, a total of 64 controls without T2DM were included.

Blinding

The patients, study staff, endoscopists and the primary outcome assessor, were blinded to treatment allocation, and the surgeons did not participate in the follow-up.

Statistical methods

Descriptive data are presented as mean (SD), median (range) or number (%). Between-group comparisons were analyzed with independent samples t-test, and Chi-Square tests for continuous and categorical variables as appropriate. All tests were two-sided and p values < 0.05 were considered statistically significant. All statistical analyses were performed using IBM SPSS 25 (SPSS Inc., Chicago, IL).

Results

Between Oct 15, 2012, and Sept 1, 2017, 319 consecutive patients with T2DM were assessed for eligibility, 194 were excluded, and 125 patients were initially enrolled and underwent a baseline examination between Jan 28, 2013, and Feb 12, 2018 (Figure 1a). Further, one patient was excluded due to undetectable c-peptide level on baseline examination, leaving 124 patients to be included (Figure1a). A total of 210 consecutive patients without T2DM scheduled for bariatric surgery between January 2016 and January 2018, were assessed for eligibility, 81 patients were invited to participate, and 64 patients were included (Figure 1b).

Patients with T2DM were on average 6 years older than those without T2DM, and a lower proportion of patients with T2DM used non-steroidal anti-inflammatory drugs as compared with patients without T2DM (Table 1). Body mass index, drinking habits, smoking habits and the proportion of patients using anti-reflux medication did not differ significantly between groups (Table 1).

GERD symptoms

The GSRS and GerdQ questionnaires were completed by 97% of patients. The proportion of patients with reflux symptoms did not differ significantly between those with or without T2DM; GSRS, 28% versus 18%, p=0.12, GerdQ, 14% versus 18%, p=0.53 (Table 2).

Esophagogastroduodenoscopy (EGD) findings

With the exception of one patient with T2DM, all patients underwent EGD. The proportion of patients with esophagitis did not differ significantly between patients with or without T2DM, 58% versus 47%, p= 0.16 (Table 2). The majority of patients with findings had less advanced erosive esophagitis (Los Angeles grade A and B), and few patients had more advanced esophagitis (Los Angeles grade C (n=3) and D (n=2). Four patients with T2DM had Barrett’s

esophagus. Hiatal hernias were diagnosed in 44% of the patients in both groups (Table 2), and the majority of patients with hiatal hernia had erosive esophagitis, 36 (67%) patients in the T2DM group and 23 (82%) patients in the non-T2DM group.

Association between erosive esophagitis and GERD symptoms

GERD-symptoms were not significantly associated with erosive esophagitis among patients with or without T2DM (Table 3). Notably, the majority of patients with esophagitis did not have GERD-symptoms (68%-80%), while the majority of patients with GERD-symptoms had esophagitis (Table 3).Both questionnaires had low sensitivities (0.20-0.33) for diagnosing endoscopic esophagitis in both groups, while their respective specificities were higher (0.76-0.94) (Table 4). Accordingly, the predictive values of negative tests were low in both groups, while the positive predictive value of GerdQ was relatively high (Table 4).

24-hour pH-metry

A total of 114 out of 124 (92%) patients with T2DM completed the 24-hour pH monitoring out of whom 111 completed questionnaires and 113 underwent EGD. Pathologic acid reflux was diagnosed in 63 patients (55%) with DeMeester score ≥14.72 including 48 patients (42%) with AET ≥6% (Table 5). Twenty of 65 T2DM patients with erosive esophagitis did not have pathologic acid reflux (Table 5), but one of these patients had borderline GERD.

Further, 45 of 63 patients (71%) with pathologic acid reflux had erosive esophagitis. In addition, 29 of 43 patients (67%) who had both pathological acid reflux and erosive esophagitis, were asymptomatic. Three of the 18 patients (17%) with GERD symptoms without erosive esophagitis had pathologic acid reflux (NERD).

Discussion

The results from the present analysis of baseline data from the Oseberg study did not confirm our hypothesis of a higher prevalence of GERD among bariatric patients with T2DM compared with those without T2DM. Further, the proportions of patients with GERD symptoms were relatively low in both groups (< 29%), while approximately half the patients in both groups had esophagitis. In addition, in agreement with previous studies (10, 19, 33), we found no significant association between GERD symptoms and erosive esophagitis in neither group. Notably, the majority of patients (both groups) with esophagitis did not have GERD-symptoms. In addition, more than half of the patients with T2DM had pathologic acid reflux, and the majority of these patients also had asymptomatic esophagitis.

Possible mechanisms and explanations

Taking into account that obesity and T2DM are independent predictors of GERD (9, 14, 34, 35), we expected a higher prevalence of GERD-symptoms and esophagitis among patients with obesity and T2DM than in those with obesity only. T2DM may increase the risk of esophagitis due to reduced amplitude of esophageal contractions, fewer peristaltic waves, decreased velocity of peristalsis, reduced lower esophageal sphincter pressure and abnormal gastroesophageal reflux (14, 36-39). Notably, the numerical proportion of patients with esophagitis in the group with T2DM was higher than in the group without T2DM, but since sample size was calculated for differences in GSRS scores, we cannot rule out that the lack of statistical significance could be caused by a type 2 error.

The high prevalence of asymptomatic GERD (erosive esophagitis) in both groups might be partly explained by esophageal hyposensitivity due to obesity, diabetes or both (40). To our knowledge, the cause of esophageal hyposensitivity in patients with obesity and / or diabetes is unknown. However, it has been shown that in patients with Barrett's esophagus who often are hyposensitive to acid reflux, the nociceptive sensory nerves are located more profound in

the esophageal mucosa (41). Accordingly, it can be speculated whether the subjects included in the present study may have deep sensory nerves, which may partly explain their esophageal hyposensitivity, but this was not assessed in the present study.

Comparison with other studies

To the best of our knowledge, our study is the first to compare the prevalence of GERD symptoms and erosive esophagitis among bariatric patients with or without T2DM. However, our finding of a low frequency of GERD symptoms confirms the results of previous studies of patients with morbid obesity (33, 35, 42) and a study of patients with diabetes (43).

In addition, our results are in accordance with previous studies among bariatric surgery candidates which have documented a high prevalence of erosive esophagitis (6, 44)

Our findings differ from the results in two previous studies which reported a high percentage of GERD symptoms among patients with morbid obesity (5, 45), but a low percentage of erosive esophagitis. However, these studies are not comparable with ours because they included younger patients and used self-reported gastrointestinal symptoms or other types of questionnaires than GerdQ and GSRS to assess GERD symptoms.

Our findings of a high prevalence of asymptomatic GERD in patients with and without T2DM, partly confirm previous studies, both from the general population and in populations with T2DM and /or obesity (22, 46). The association between GERD symptoms, as assessed by the validated questionnaires, and erosive esophagitis has been shown to be weak by others (10, 19, 33). Our findings also support other studies demonstrating a poor association between GERD symptoms and pathologic acid reflux (10, 47), suggesting that most acid reflux events may be asymptomatic in patients with severe obesity. In line with the high frequency of asymptomatic esophagitis and acid reflux, only three patients had NERD in our study. Interestingly, 20 of 65 T2DM patients with erosive esophagitis did not have pathologic acid reflux, and only one of these had borderline GERD. This finding is in contrast with Kristo et

al. (46), who reported a high proportion of borderline GERD among patients with esophagitis. In addition, duodeno-gastro-esophagal reflux of bile may partly explain our findings of erosive esophagitis in patients without acid reflux (48) but bile reflux was not assessed in the present study.

Our study has some limitations. Most patients were of Caucasian origin, with a majority of women (68%), and the results may not be generalizable to other ethnicities. The comparative groups were non-matched, resulting in groups that differed in age and use of NSAIDs. Increasing age is risk factor for GERD, and older patients may underreport reflux symptoms (49).

Conclusion

Our results suggest that the prevalence of GERD in patients scheduled for bariatric surgery is similar in patients with or without T2DM, and that the proportion of patients with asymptomatic GERD is high independent of the presence or absence of diabetes. Accordingly, GERD may be underdiagnosed in patients not undergoing a preoperative endoscopy or acid reflux assessment.

Conflict of interest

All authors declare that they have no conflict of interest.

Ethical Approval Statement

All procedures performed in studies involving human participants 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.

Statement of informed consent

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

Table 1 Demographic and clinical characteristics in candidates for bariatric surgery with or without type 2 diabetes mellitus (T2DM)

	T2DM (n=124)	Non-T2DM (n=64)	*p* value
Age, years (SD)	48.6 (9.4)	43.0 (11.0)	0.001[a]
Gender, female, no. (%)	81 (65)	46 (72)	0.46[b]
Ethnicity, Caucasian, no. (%)	117 (96)	64 (100)	0.24[b]
Weight, kg (SD)	125.6 (21.8)	127.2 (20.1)	0.63[a]
Body mass index, BMI, kg/m^2 (SD)	42.3 (5.5)	43.0 (5.0)	0.46[a]
Current smoker, no. (%)	14 (11)	4 (6)	0.34[b]
Alcohol consumption (units per week)	0 (0-8)	1 (0-3)	0.13[b]
Use of anti-reflux medication, no. (%)	35 (29)	12 (19)	0.23[b]
Proton pump inhibitors, no. (%)	34 (27)	11 (17)	NA
Histamine receptor antagonists, no. (%)	1 (0.8)	1 (1.6)	NA
Use of NSAID, no. (%)*	14 (11)	20 (32)	0.001[b]
Duration of diabetes, years (SD)	6.4 (6.0)	NA	NA
Diabetes complications, no. (%)**	13 (12)	NA	NA

Data are presented as observed mean (SD), median (range) or no. (%) of patients
[a] Independent samples t-test
[b] Chi-Square test
* NSAID used due to self-reported co-morbidities like skeletal-muscle- and arthritis-disorders
** Retinopathy, neuropathy, or nephropathy (albuminuria)

Table 2 GERD symptoms, endoscopic findings and 24-hour ambulatory pH-metry among bariatric candidates with or without type 2 diabetes mellitus (T2DM)

	T2DM (n=123)	non-T2DM (n=64)	*p* value
GSRS-R-score ≥20, no. (%)*	34 (28)	11 (18)	0.17[b]
GerdQ-score ≥8, no. (%)*	17 (14)	11 (18)	0.68[b]
GSRS-R-score, mean (SD) *	13.2 (16.9)	9.0 (14.0)	0.09[a]
GerdQ-score, mean (SD)*	6.3 (1.84)	6.3 (1.62)	0.91[a]
Esophagitis, no. (%)**	71 (58)	30 (47)	0.21[b]
LA grade A, no. (%)	41(33)	18 (28)	0.64
LA grade B, no. (%)	27 (22)	10 (16)	
LA grade C, no. (%)	2 (2)	1(2)	
LA grade D, no. (%)	1 (0.8)	1(1.6)	
Barrett's esophagus, no. (%)	4 (3)	0	0.36
Hiatal hernia ≥ 2cm, no. (%)	54 (44)	28 (44)	1.0[b]
Hiatal hernia ≥ 5cm, no. (%)	4 (3)	0	0.14[b]
Peptic ulcer, no. (%)	7 (6)	8 (13)	0.18[b]
DeMeester score, mean (SD)***	24 (22)	NA	NA
pH < 4, % of time (AET) (SD)***	6.42 (6.61)	NA	NA

Data are presented as observed mean (SD), or no. (%) of patients
[a] Independent samples t-test
[b] Chi-Square test
AET = distal esophageal acid exposure time
* T2DM n=120, non-T2DM n=62
** T2DM n=123, non-T2DM n=64
*** T2DM n=114

Table 3 Association between erosive esophagitis (any grade) and GERD symptoms among bariatric candidates with or without T2DM

			Erosive esophagitis					
			T2DM-group (n=120)			Non-T2DM-group (n=62)		
			Yes (n=69)	No (n=51)	*p* value	Yes (n=28)	No (n=34)	*p* value
GERD symptoms	GSRS-Reflux ≥20	Yes no. (%)	22 (32)	12 (24)	0.42[a]	6 (21)	5 (15)	0.72[a]
		No no. (%)	47 (68)	39 (76)		22 (79)	29 (85)	
	GerdQ ≥8	Yes no. (%)	14 (20)	3 (6)	0.05[a]	8 (29)	3 (9)	0.09[a]
		No no. (%)	55 (80)	48 (94)		20 (71)	31 (91)	

Data are presented as no. (%) of patients
[a] Chi-Square test

Table 4.
Sensitivity, specificity, positive predictive value and negative predictive value of GSRS≥20 and GerdQ ≥ 8 for detection of endoscopic esophagitis among bariatric candidates with or without T2DM

	GSRS-Reflux		GerdQ	
	T2DM	non-T2DM	T2DM	non-T2DM
Sensitivity	0.33	0.21	0.20	0.28
Specificity	0.76	0.85	0.94	0.91
Positive predictive value	0.65	0.55	0.82	0.72
Negative predictive value	0.45	0.57	0.46	0.60

Table 5. Association between pathologic acid reflux, GERD symptoms and esophagitis among bariatric candidates with T2DM.

			Pathological acid reflux (DeMeester score)			**Pathological acid reflux (AET)**		
			No reflux (<14.72)	Reflux (≥14.72)	*p* value	No reflux (<6%)	Reflux (≥6%)	*p* value
GERD symptoms	GSRS-Reflux ≥20	Total	49	62		64	47	
		Yes n (%)	13 (27)	19 (31)	0.79[a]	17 (27)	15 (32)	0.69[a]
		No n (%)	36 (73)	43 (69)		47 (73)	32 (68)	
	GerdQ ≥8	Yes n (%)	5 (10)	10 (16)	0.53[a]	7 (11)	8 (17)	0.52[a]
		No n (%)	44 (90)	52 (84)		57 (89)	39 (83)	
Erosive esophagitis		Total	50	63		65	48	
		Yes n (%)	20 (41)	45 (71)	0.002[a]	32 (49)	33 (69)	0.06[a]
		No n (%)	30 (59)	18 (29)		33 (51)	15 (31)	

Data are presented as number (%) of patients
AET = distal esophageal acid exposure time
[a] Chi-Square test

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