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Impact of cardiovascular risk factors on chronic abdominal pain after laparoscopic gastric bypass

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ABSTRACT

INTRODUCTION: Patients with chronic pain after laparoscopic Roux-en-Y gastric bypass (LRYGB) surgery frequently report intense postprandial abdominal pain. Reduced blood supply due to atherosclerosis was hypothesised to be a contributing cause.

METHODS: This was a retrospective, single-centre cohort study including all patients with LRYGB surgery from 2010 through 2015. Data from multiple registries, medical records and a questionnaire were used. The risk of chronic abdominal pain was analysed using multivariate logistic regression.

RESULTS: We included 787 patients. Among these, 177 (23%) patients were defined as having chronic abdominal pain. The median follow-up was 63 months. When investigating the impact of risk factors for atherosclerosis including dyslipidaemia, Type 2 diabetes, hypertension, smoking and cardiovascular co-morbidities, the "atherosclerosis composite score" was a significant risk factor (odds ratio = 1.22, 95% confidence interval: 1.02-1.45). In a multivariate model specifically investigating dyslipidaemia, the association with chronic abdominal pain was non-significant.

CONCLUSIONS: In this exploratory study, development of chronic abdominal pain was significantly associated with risk factors for atherosclerosis, but the specific association with dyslipidaemia was non-significant.

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TRIAL REGISTRATION: The study was approved by the Danish Data Protection Agency (No. REG-063-2017).

The indication for bariatric surgery in Denmark is a BMI > 35 kg/m^2 in combination with an obesity-related co-morbidity or significant risk of development hereof. This leads to a high prevalence of obesity-related co-morbidities and a high risk of concurrent cardiovascular disease among candidates for bariatric surgery.

Long-term complications are frequent and contribute to high costs in the post-operative period after laparoscopic Roux-en-Y gastric bypass (LRYGB) surgery, and chronic abdominal pain in particular has been shown to have a negative impact on quality of life [1, 2]. The majority of these patients report intense upper and postprandial abdominal pain without being able to determine the cause. These symptoms may imitate abdominal angina and could in theory be explained by atherosclerosis and subsequently reduced microcirculation [3, 4]. If atherosclerosis increases the risk of chronic post-operative pain, risk factors for atherosclerosis should also be associated with pain. Previous studies associated atherosclerosis and cardiovascular co-morbidities specifically with dyslipidaemia and with further risk factors including Type 2 diabetes (T2D), hypertension and smoking [5-8].

Dyslipidaemia and other risk factors for atherosclerosis were therefore hypothesised to be associated with chronic post-operative abdominal pain. This exploratory study aimed to investigate this association among patients receiving LRYGB surgery.

METHODS

This was a retrospective cohort study including all patients undergoing LRYGB surgery at the Zealand University Hospital in Denmark from 2010 through 2015. The indication for LRYGB surgery followed national guidelines. All Danish residents are registered in the Civil Registration System with a personal identification number, which enabled linkage of data from multiple sources [9]. The cohort has previously been used for identification of the prevalence and risk factors for chronic abdominal pain as well as quality of life and occupational outcomes [2, 3].

Diagnosis codes according to the International Classification of Diseases (ICD)-10 were obtained from the Danish National Patient Register. The Charlson Comorbidity Index was calculated based on ICD-10 codes [10]. Cardiovascular co-morbidity was defined as a composite of myocardial infarction (I21-I23), congestive heart failure (I50, I11.0, I13.0, I13.2), peripheral vascular disease (I70-I74, I77) and cerebrovascular disease (I60-I169, G45, G46). Data were obtained from the Danish National Prescription Register on pre- and post-operative use of strong analgesics including the Anatomical Therapeutic Chemical codes N02 (analgesics), N03 (antiepileptics) and N06 (antidepressants). From Statistics Denmark, information regarding marital status, highest attained educational level and occupational status was obtained. Data regarding preoperative co-morbidities, smoking and occupational status were systematically registered in the Danish Obesity Surgery Register. Medical records supplemented the registries with detailed information on preoperative co-morbidities, smoking, alcohol consumption and occupational status. Self-reported abdominal pain for assessment of chronic abdominal pain was obtained through a questionnaire [3].

Definition of dyslipidaemia

Dyslipidaemia was defined as altered or increased levels of cholesterol, subfractions of

cholesterols or triglycerides. Tolerable levels were assessed according to national treatment guidelines from the Danish Cardiology Society [11]. All patients were screened for obesity-related co-morbidities including dyslipidaemia by an endocrinologist in the bariatric centre. Dyslipidaemia was preferably defined from medical records, otherwise from the Danish Obesity Register. If neither were available, dyslipidaemia was defined from the Danish National Patient Register by ICD-10 E78.

Definition of chronic abdominal pain

Chronic abdominal pain was defined as a composite of post-operative initiation or escalation of strong analgesics (including opioids or opioid analogues, gabapentin, pregabalin or tricyclic antidepressants), a diagnosis with chronic pain, a referral to a specialised pain clinic or if patients reported having abdominal pain more than twice weekly within the past month in the study questionnaire.

Statistics

Categorical variables were analysed using the χ^2-test. Normally distributed continuous variables were analysed using the two-sample t-test; otherwise the Mann-Whitney U test was used. The risk of chronic abdominal pain was explored using logistic regression and was presented as odds ratios (OR) with 95% confidence intervals (95% CI). $p < 0.05$ were considered significant.

Model 1 investigated the association with dyslipidaemia. The constructed model was adjusted for age, sex, BMI, marital and occupational status, smoking, T2D, hypertension, obstructive sleep apnoea, polycystic ovarian syndrome, arthrosis, cardiovascular co-morbidities, preoperative use of strong analgesics and psychiatric disorder.

Model 2 investigated the impact of factors known to be associated with atherosclerosis. These factors were pooled in an “atherosclerosis composite score” consisting of smoking, dyslipidaemia, T2D, hypertension and cardiovascular co-morbidities including myocardial infarction, congestive heart failure, peripheral vascular disease and cerebrovascular disease. The score served as a continuous variable ranging from zero to eight with each factor contributing with one point. The constructed model was further adjusted for age, sex, BMI, marital and occupational status, preoperative use of strong analgesics and psychiatric disorder.

Patients with missing data were not included in the analyses. Statistical analyses were performed.

Trial registration: The study was approved by the Danish Data Protection Agency (No. REG-063-2017).

RESULTS

In total, 800 patients underwent LRYGB surgery from 2010 through 2015. Patients were excluded if either deceased (n = 5), emigrated (n = 4) or unavailable for follow-up due to lack of a registered permanent address (n = 4). Consequently, 787 patients were included in the study. The median

follow-up was 63 months.

Medical records were available for 660 (84%) patients and 532 (68%) patients answered the study questionnaire. For three (< 0.01%) patients, data were neither available through medical records nor via the Danish Obesity Surgery Register. Data completeness for register data was 99.5% and completeness across all sources was 94%.

Among the 34 (4%) patients who were re-operated within 30 days, nine patients underwent laparoscopy and one patient underwent gastroscopy, all without pathological findings. Overall, 177 (23%) patients were defined as having chronic abdominal pain. The "atherosclerosis composite score" was similar for patients with and without chronic abdominal pain (median = 1, range: 0-3 for both groups), but the difference was significant (p = 0.0003). The prevalence of dyslipidaemia (p = 0.001), hypertension (p = 0.005), smoking (p = 0.003) and cardiovascular co-morbidities (p = 0.024) was higher among patients with chronic pain, whereas there was no difference for T2D (p = 0.514). Baseline characteristics are presented in **Table 1**.

TABLE 1 / Characterisation of patients with and without post-operative chronic abdominal pain.

	Chronic pain (N = 177)	No chronic pain (N = 610)	p-value
Age at the time of surgery, yrs, median (IQR)	42 (36-49)	40 (34-47)	0.006
Sex, n (%)			0.816
Female	141 (79.7)	481 (78.9)	
Male	36 (20.3)	129 (21.2)	
Preoperative BMI, kg/m^2, median (IQR)[a]	42.2 (40.0-46.7)	44.7 (41.2-49.2)	< 0.0001
Marital status, n (%)			0.616
Married or cohabiting	121 (68.4)	429 (70.3)	
Single	56 (31.6)	181 (29.7)	
Educational level, n (%)[b, d]			0.491
Pre-primary	1 (0.60)	2 (0.33)	
Primary school or equivalent	49 (29.2)	188 (31.2)	
Secondary or vocational education	94 (56.0)	301 (50.0)	
Short-cycle higher education	5 (3.0)	17 (2.8)	
Bachelor or equivalent	19 (11.1)	86 (14.3)	
Master or equivalent	-	8 (1.3)	
PhD or other research education	-	-	
Occupational status, n (%)			< 0.0001
Employed	107 (60.5)	456 (74.8)	
Unemployed or retired	70 (39.6)	154 (25.3)	
Smoking history, n (%)[a]			0.003
Smoking	54 (30.5)	137 (22.5)	
Never or previously smoking	122 (68.9)	471 (77.1)	
Consumption of alcohol, n (%)[c, e]			0.446
Low: female < 7 U/wk, male < 14 U/wek	146 (96.7)	474 (98.3)	
Moderate: female 7-14 U/wk, male 14-21 U/wk	4 (2.7)	6 (1.2)	
High: female >14 U/wk, male > 21 U/wk	1 (0.7)	2 (0.4)	
Charlton Comorbidity Index	0 (0-3)	0 (0-7)	0.012
Cardiovascular co-morbidities, n (%)			
Myocardial infarction	2 (1.1)	1 (0.2)	0.066
Congestive heart failure	1 (0.6)	6 (1.0)	0.602
Peripheral vascular disease	1 (0.6)	2 (0.3)	0.652
Cerebrovascular disease	5 (2.8)	1 (0.2)	0.0003
Subtotal	8 (4.5)	10 (1.6)	0.024
Obesity-related co-morbidities, n (%)[a]			
Hypertension	59 (39.2)	171 (28.1)	0.005
Type 2 diabetes	42 (23.9)	131 (21.6)	0.514
Obstructive sleep apnoea	18 (10.2)	58 (9.5)	0.786
Polycystic ovarian syndrome	10 (5.7)	64 (10.5)	0.053
Arthrosis	51 (29.0)	121 (19.9)	0.010
Dyslipidaemia	48 (27.1)	99 (16.2)	0.001
Other co-morbidities, n (%)			
Preoperative use of strong analgesics	53 (29.9)	56 (9.2)	< 0.0001
History of psychiatric disorder[a]	67 (38.3)	176 (29.0)	0.020

IQR = interquartile range.
a) n = 784, patients with missing data were not included.
b) n = 712, patients with missing data were not included.
c) n = 677, patients with missing data were not included.
d) According to the DISCED-15 classification.
e) 1 U = 12 g alcohol.

Multivariate analyses

Model 1 resulted in a non-significantly increased risk of chronic abdominal pain among patients

with dyslipidaemia (OR = 1.36, 95% CI: 0.83-2.24). Model 2 showed a significant impact by the "atherosclerosis composite score" on the risk of chronic abdominal pain (OR = 1.22, 95% CI: 1.02-1.45). Multivariate models are presented in **Table 2**.

TABLE 2/ Risk factors for development of post-operative chronic abdominal pain assessed by multivariate analyses.

	OR (95% CI)	
	model 1[a] (N = 784)	model 2[b] (N = 784)
Age at the time of surgery	1.01 (0.98-1.03)	1.01 (0.99-1.03)
Sex		
Female	1.02 (0.62-1.66)	1.02 (0.64-1.61)
Male	1 (reference)	1 (reference)
Preoperative BMI	0.95 (0.92-0.98)	0.95 (0.92-0.98)
Marital status		
Married or cohabiting	1 (reference)	1 (reference)
Single	1.23 (0.82-1.84)	1.23 (0.83-1.84)
Occupational status		
Employed	1 (reference)	1 (reference)
Unemployed or retired	1.48 (0.98-2.24)	1.44 (0.96-2.17)
Smoking history		
Smoking	1.26 (0.84-1.90)	-
Never or previously smoking	1 (reference)	-
Cardiovascular co-morbidities[c]	2.17 (0.77-6.08)	-
Atherosclerosis composite score[d]	-	1.22 (1.02-1.45)
Obesity-related co-morbidities		
Hypertension	1.35 (0.88-2.07)	-
Type 2 diabetes	0.81 (0.49-1.32)	-
Obstructive sleep apnoea	0.94 (0.49-1.78)	-
Polycystic ovarian syndrome	0.59 (0.28-1.24)	-
Arthrosis	1.05 (0.67-1.65)	-
Dyslipidaemia	1.36 (0.83-2.24)	-
Other co-morbidities		
Preoperative use of strong analgesics	2.18 (1.55-3.07)	2.30 (1.65-3.21)
History of psychiatric disorder	1.19 (0.80-1.78)	1.17 (0.79-1.74)

CI = confidence interval; OR = odds ratio.
a) Adjusted for age, sex, BMI, marital status, occupational status, smoking, cardiovascular co-morbidities, hypertension, Type 2 diabetes, obstructive sleep apnoea, polycystic ovarian syndrome, arthrosis, dyslipidaemia, preoperative use of strong analgesics and psychiatric disorder.
b) Adjusted for age, sex, BMI, marital status, occupational status, smoking, atherosclerosis score, preoperative use of strong analgesics and psychiatric disorder.
c) Composite of myocardial infarction, congestive heart failure, peripheral vascular disease and cerebrovascular disease.
d) Consists of smoking, dyslipidaemia, Type 2 diabetes, hypertension, myocardial infarction, congestive heart failure, peripheral vascular disease and cerebrovascular disease; range: 0-6 with each factor contributing with 1 point.

When repeating model 1 and model 2 in a subgroup with exclusion of patients who were re-operated within 30 days, the impacts of dyslipidaemia (OR = 1.28, 95% CI: 0.76-2.25) and the "atherosclerosis composite score" (OR = 1.23, 95% CI: 1.02-1.47) remained unchanged.

DISCUSSION

In this exploratory study, development of chronic abdominal pain was significantly associated with an "atherosclerosis composite score" consisting of risk factors associated with atherosclerosis including smoking, dyslipidaemia, T2D, hypertension and cardiovascular co-morbidities. The specific association with dyslipidaemia was non-significant.

The association between chronic abdominal pain and risk factors for atherosclerosis has not been investigated previously; nor have associations with intra- or post-operative changes in intestinal microcirculation. In previous studies, patients with chronic abdominal pain described intense upper and postprandial abdominal pain, which may imitate the symptoms of abdominal angina [3, 4]. This triggered the hypothesis of possible localised mesenteric ischaemia due to compromised intestinal microcirculation.

Cardiovascular disease is known to increase the risk of chronic pain, which supported the hypothesis of atherosclerosis as a contributing cause for post-operative chronic abdominal pain [12]. The "atherosclerosis composite score" was created based on previously identified risk factors for atherosclerosis including dyslipidaemia, T2D, hypertension and smoking as well as cardiovascular co-morbidities likely to be caused by atherosclerosis [5-8]. Specifically, previous studies showed an effect of dyslipidaemia on both cerebral and myocardial microcirculation and perfusion. They also associated dyslipidaemia with chronic low back pain, which was explained by atherosclerosis in the aorta and arteries supplying the lower part of the spine leading to reduced blood supply and disc damage [13-16].

As the cause of chronic abdominal pain is multifactorial, the complexity of the associations required adjustment for additional confounders. Adjustment for preoperative use of strong analgesics and unemployment was based on previously established associations with chronic abdominal pain, whereas the impact of interpersonal status and psychiatric co-morbidities has been investigated only for weight loss and quality of life [2, 3, 17, 18]. The risk of confounding by indication was minimised by adjusting for BMI and obesity-related co-morbidities.

Our study is not without limitations. A post-hoc power analysis revealed that with a prevalence of dyslipidaemia within the groups of 27% and 16%, respectively, 218 patients would be needed in each group to achieve a significant difference. This limitation may possibly explain the non-significant result when specifically investigating the impact of dyslipidaemia simultaneously with the significant result when pooling risk factors for atherosclerosis.

Lack of information on duration, pre-and post-operative levels of serum-lipids and treatment with lipid-lowering drugs made us unable to distinguish between severities of dyslipidaemia.

Information on T2D and hypertension lacked similar details. As these co-morbidities are associated with cardiovascular co-morbidities, patients with prolonged duration, poor regulation and lack of treatment may have an increased risk of developing post-operative chronic pain [12]. In addition, inclusion of lipid lowering drugs would be interesting as one could imagine a beneficial effect of statins attributable to their previously shown anti-inflammatory effects [19].

The aim of this study was to identify preoperative risk factors. Therefore, post-operative complications were not included in the primary multivariate models. As early complications have previously been linked to chronic abdominal pain [3], subgroup analyses with exclusion of patients who underwent reoperation within 30 days were made. These analyses indicated an unchanged impact of dyslipidaemia and the "atherosclerosis composite score" in the development of chronic abdominal pain. Long-term complications such as operations for incisional hernia, stenosis, adhesions and non-acute closures of mesenteric defects were significantly associated with decreased quality of life. The association between long-term complications and chronic pain have not yet been investigated, but the decrease in quality of life indicates a minimal effect of these interventions on abdominal pain [2]. As a consequence of not considering long-term complications and not categorising the patients according to pain characteristics and intensity, patients with chronic abdominal pain constituted a non-unanimous population, which is a substantial limitation. The specific definition of chronic pain used in this study has not been validated. However, the definition was adapted from a previous study which achieved a high sensitivity and specificity by combining the use of strong analgesics, diagnosis codes and self-reporting to define chronic pain [20].

Limitations related to the definition of chronic pain, the study questionnaire and the use of registries have been described in a previous study [3].

The strengths of the present study included the use of national registries with a data completeness of 99.5% for both pre- and post-operative data. The register-based design ensured long national follow-up without missing data, whereas use of medical records and questionnaires provided detailed data at an individual level.

Due to the limitations and lack of external validity, the results reflect preliminary outcomes and should be considered hypothesis-generating input for larger prospective studies. These studies should use standardised definitions and detailed characterisations of chronic pain and should include pre- and post-operative levels of serum-lipids, blood pressure and fasting glucose to adjust for current status of co-morbidities and to determine a dose-response effect. Furthermore, inclusion of treatment with lipid-lowering, antihypertensive and antidiabetic treatment is essential. Such studies could justify clinical intervention studies investigating, e.g., different types of bariatric surgery and pathophysiologic factors and could increase the focus on elucidation and treatment of risk factors for compromised microcirculation prior to bariatric surgery.

CONCLUSIONS

In this exploratory study, development of chronic abdominal pain was significantly associated with risk factors for atherosclerosis, but the specific association with dyslipidaemia was non-significant.

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LITERATURE

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