

Risk of Thromboembolic Complications in Morbidly Obese Patients Treated with Laparoscopic Bariatric Surgery

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Abstract

Purpose: The obesity is a metabolic disturbance which is associated with blood hypercoagulability. The purpose of the study was to evaluate if the bariatric procedure increases the risk of thromboembolic complications in morbidly obese patients.

Methods: The study involved 38 patients with BMI over 35 who underwent laparoscopic gastric banding. The reference group consisted of 30 surgical patients. The following parameters were examined: Tissue Factor (TF) antigen (TF: Ag) and activity (TF: Ac), its inhibitor - Tissue Factor Pathway Inhibitor (TFPI) antigen (TFPI: Ag) and activity (TFPI: Ac), concentration of thrombin/antithrombin complexes (TAT) and activity of antithrombin (AT).

Results: Bariatrics patients had significantly higher levels of TF: Ag (151,9)($p < 0.04$) and TF: Ac (1,42)($p < 0.05$) in comparison with reference group (91,3 and 0.1 respectively). Similar was with TFPI, where its TFPI: Ag (85,3) TFPI: Ac (1.16) were higher compared to reference group (67.3 and 1.1 respectively) however the differences did not reach statistically significant level. The level of TAT complexes was also significantly higher in morbidly obese patients (16,7 vs 8.3) ($p < 0.031$) but the activity of AT III was similar in both groups. Based on above in morbidly obese patients a hypercoagulable state can be recognized which was caused by TF. After procedure TF:Ag was almost in the same level as before with the same tendency to reference group ($p < 0.05$) however IF:Ac was insignificant lower ($p < 0.48$). Similar tendency was observed with other parameters which was an evidence for persistent hypercoagulable state despite of a postoperative decrease of TF activity ($p < 0.27$). This means that the bariatric procedure did not influence on blood coagulation of morbidly obese patients. In multivariate regression analysis was shown that only BMI, history of deep vein thrombosis or history of pulmonary complications are an independent factor of postoperative complications connecting with haemostasis.

Conclusions: Laparoscopic bariatric procedures are not at increased risk of thromboembolic complications in morbidly obese patients.

Keywords: Thromboembolic complications; Morbid obesity; Bariatric surgery

Introduction

Obesity is a metabolic disease which badly restrict the quality of life and often leads to death. One of cause of death is blood hypercoagulability of the morbidly obese. Such complications as myocardial infarction, stroke and venous thromboembolism which can be observed in those patients are mainly connected with hypercoagulability [1-8]. One of the most potent activator of the coagulation process of extrinsic pathway is tissue factor (TF -Tissue Factor) [9-11]. The powerful and the only inhibitor of the extrinsic blood coagulation pathway is tissue factor pathway inhibitor (TFPI - Tissue Factor Pathway Inhibitor). A majority of the total vascular pool of TFPI and TF is bound to the vessel wall. It was revealed that a low concentration of TFPI in blood is a risk factor for thrombosis [12-14].

Many surgical procedures cause an activation of the blood coagulation system [3,8]. The laparoscopic bariatric procedures are regards as a potent factor of an increased risk of thrombosis [15,16]. The aim of the study was to evaluate if the bariatric procedure itself increases the risk of thromboembolic complications in morbidly obese patients.

Material and Methods

The study comprised 38 patients with a value of BMI > 35 kg/m² previously treated at the Clinic of Balneology and Metabolic Disorders in Ciechocinek, the Nicolaus Copernicus University in Toruń. The morbidly obese patients (BG - Bariatric Group) underwent laparoscopic adjustable gastric banding (LAGB) at the Department of General,

Vascular and Endocrinological Surgery of the Nicolaus Copernicus University Hospital in Bydgoszcz. The inclusion criteria to the project was BMI over 35 and obtaining the informed consent of each patient.

The reference group consisted of 30 surgical patients (RG-Reference Group) with BMI under 35 who were undergone laparoscopic cholecystectomy or laparoscopic appendectomy. The patients from reference group were operated in the Department of General Surgery and Transplantology of the Pomeranian Medical university in Szczecin, Poland.

Detailed analysis including BMI, the number of patients undergoing, and other epidemiological characteristics of the examined groups are presented in Table 1. The blood samples from the patients were taken before surgery and one day after surgery.

Blood plasma samples were analysed with the enzyme-linked immunosorbent assay (ELISA) for the levels of tissue factor antigen

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(TF: Ag), tissue factor pathway inhibitor (TFPI: Ag) and thrombin-antithrombin complex (TAT). The activity of tissue factor (TF: Ac) and activity of tissue factor pathway inhibitor (TFPI: Ac) were evaluated using reagents from American Diagnostical (USA). The activity of antithrombin (AT) was determined by the colorimetric method using chromogenic substrates, a coagulometer, and reagents from Bio-Ksel (Poland). The lab reference value of antigen TF and TFPI is 10 pg/mL and 89.5 ng/mL respectively. The lab value of activity TF and TFPI is 1 pM/l and 1 U/ml respectively. The reference lab value of TAT complexes is 4.0 ng/mL and antithrombin 80-120%.

Ethical Committee of Pomeranian Medical University approved the project. All subjects after having read the information leaflet about the study gave informed consent to participate in the project. The study protocol was also approved by the Bioethics Committee of Collegium Medicum in Bydgoszcz, the Nicolaus Copernicus University in Toruń.

Statistical Analysis

Statistical analysis was performed with the use of STATISTICA 10.0 software from StatSoft. Normality of distribution was assessed with the Shapiro-Wilk test. Differences between parameters characterised by normal distribution were described with mean (M) and standard deviation (SD). The parameters without characteristic of normal distribution were presented as median (Me), the first quartile (Q1) and the third quartile (Q3). t-Student's test for paired samples was used to analyse variables with normal distribution. For other without normality of distribution the Wilcoxon test was applied. Analyzing of correlation was made according to Pearson. The ANCOVA test was utilized to correct for confounding and increase of precision of an estimated differences. The p-values < 0.05 were considered as significant.

Result

Before surgical procedures patients with morbid obesity had significant higher mediana of TF: Ag and their activity of TF: Ac compared to reference group (151.9 vs 91.3 and 1.4 vs 0.0, p<0.04 and

p<0.05 respectively). Similar was with TFPI where in patients with morbid obesity had non-significantly higher levels of antigen (TFPI: Ag) and activity of TFPI: Ac (85.3 vs 67.3 and 1.2 vs 1.1 respectively). The level of TAT complexes was significantly higher compared to the reference group (16.7 vs 8.3 p<0.031) (Table 2). The average activity of antithrombin was lower non significantly compared to patients from reference group (108 ± 24 vs 118 ± 22) (Table 3).

After surgical procedures patients with morbid obesity had significantly higher mediana of TF: Ag but their activity of TF: Ac was not significantly compared to reference group (151.7 vs 93.3 and 0.68 vs 0.4, p<0.05 and p<0.27 respectively). Similar tendency was observed with TFPI both antigen and activity were higher but not statistical significance (82.3 vs 51.3 and 1.22 vs 0.9 respectively). The concentration of TAT's complexes after bariatric procedures was significantly higher compared to laparoscopic procedures (17.5 vs 11.3, p<0.041) (Table 4). The average postoperative activity of antithrombin in morbidly obese patients was lower compared to patients from reference group (100 ± 22 vs 102 ± 19 respectively) but the differences did not reach statistical significance level (p<0.7261) (Table 5). In both groups, there were signs of activation of the coagulation system but in group of bariatric procedures its intensity was much higher. The reasons for this hypercoagulable state in both groups should be sought in the tissue activator (TF), which its level was much higher compared to normal lab value. Much intensity of activation of blood coagulation in group of bariatric procedures was confirmed by a much-increased concentration of TF and TAT complexes in postoperative blood plasma samples of these patients. In the bariatric group symptoms of DVT were observed in four patients. Myocardial infarction and the pulmonary thromboembolic symptoms were also encountered. Fortunately, in the patients with morbid obese no one died in postoperative time. In the group of surgical patients operated because of aneurysm, appendicitis or cholecystolithiasis in one was recognized DVT. Like bariatric patients no deaths were observed (Table 6).

Based on above results can be got to conclusions that in

Characteristic	Study group n=38	Reference group n=30
Age [years]	38.0	56.0
Body height [cm]	170.5	178.0
Body weight [kg]	138.5	73.3
BMI [ratio]	47.8	24.6
Smokers	10	26
Hypertension	15	15
Type 2 diabetes mellitus	13	14
History of DVT	9	3
History of pulmonary complications	3	0
LDL cholesterol [mg/dl]	143.0 ± 50.0	125 ± 10.0
HDL cholesterol [mg/dl]	51.0 ± 8.0	69.0 ± 20.0
Total cholesterol [mg/dl]	225 ± 40.0	174 ± 15.0

Table 1: Characteristics of selected clinical parameters of patients with obesity vs controls.

Examined parameter	Mediana		p	Q ₁		Q ₃	
	Patients	Reference		Patients	Reference	Patients	Reference
TF:Ag [pg/mL]	151.9	91.3	0.04	130.1	118.6	218.3	198.9
TF:Ac [pM/l]	1.4	0.1	0.05	0.31	0.0	3.9	7.9
TFPI:Ag [ng/mL]	85.3	67.3	0.23	48.6	40.6	114.2	95.7
TFPI:Ac [U/ml]	1.2	1.1	0.61	0.94	1.1	1.4	1.89
TAT [ng/ml]	16.7	8.3	0.031	10.1	2.89	27.5	23.9

Table 2: The preoperative mediana of examined parameter in bariatric (Patients) and reference patients (Reference) without normal distribution (Q₁ – the first quartile, Q₃ – the third quartile, p – statistical significance according to Wilcoxon test).

The examined parameter	Bariatric group	Reference group	p
	X ± SD	X ± SD	
	n = 38	n = 30	
AT [%]	108.6 ± 24	118 ± 22	0.6161

Table 3: The preoperative activity of antithrombin (AT) with normal distribution in bariatric and reference patients (X – mean, SD – standard deviation, p – statistical significance according to Student's t - test).

Examined parameter	Mediana		p	Q ₁		Q ₃	
	Patients	Reference		Patients	Reference	Patients	Reference
TF:Ag [pg/mL]	151.7	93.3	0.05	94.9	58.6	219.1	208.9
TF:Ac [pMol/l]	0.68	0.4	0.27	0.00	0.0	7.35	9.9
TFPI:Ag [ng/mL]	82.3	51.3	0.73	61.6	36.3	112.9	125.1
TFPI:Ac [U/ml]	1.22	0.9	0.71	0.76	0.1	1.4	1.18
TAT [ng/ml]	17.5	11.3	0.041	12.76	5.89	33.82	23.9

Table 4: The postoperative mediana of examined parameter in bariatric (Patients) and reference patients (Reference) without normal distribution (Q₁ – the first quartile, Q₃ – the third quartile, p – statistical significance according to Wilcoxon test).

The examined parameter	Bariatric group	Reference group	p
	X ± SD	X ± SD	
	n = 38	n = 30	
AT [%]	100.4 ± 22	102 ± 19	0.7631

Table 5: The postoperative activity of antithrombin (AT) with normal distribution in bariatric and reference patients (X – mean, SD – standard deviation, p – statistical significance according to Student's t - test).

Type of clinical form of thrombosis	Bariatric group	Reference group
DVT	4	1
Myocardial infarction	2	0
Pulmonary thromboembolism	1	0
Other	0	0

Table 6: Clinical form of postoperative thrombosis in the examined group of patients (DVT – deep venous thrombosis, MI – myocardial infarction, PT – pulmonary thromboembolism, Other – for example sudden death).

morbidly obese patients after an operation there is an increased risk of thromboembolic complications. But in multivariate regression analysis was shown that only the BMI, the preoperative history of DVT and pulmonary thromboembolism are as independent factors of an increased risk of postoperative thrombosis.

In multivariate regression analysis was proved that bariatric laparoscopic procedures are not at increased risk of postoperative thrombosis. The conclusion should be that bariatric procedures are not at increased risk of postoperative thrombosis and they can be recommend in treatment of morbidly obese patients.

Discussion

The study demonstrated that patients with morbid obesity had higher both antigen and activity of TF compared to other surgical patients. What seems interesting that morbidly obese patients had antigen and activity of TFPI in normal lab range. In both groups the concentrations of TAT complexes were above to normal lab range but in bariatric one was significantly higher in comparison with reference (p<0.031). It was an evidence of activation of blood coagulation process where in bariatric group the intensity of this activation was much greater. An increased amount of TF in the blood of patients with morbid obese can be regarded as a cause of this much greater hypercoagulable state.

Unfortunately, in literature there are a limited number of publications dealing with blood coagulation process and impact of the surgery on it in patients with morbid obesity. A study by Kopp et al. carried out on 37 morbidly obese patients, like our study, demonstrated an over 2-fold higher baseline level of TF but TFPI level was slightly

lower [17]. In another study Knopp et al. in analysed 36 patients with morbid obesity reported already similar levels of both TF and TFPI [18]. Ay et al. revealed an increased activity of TF in microparticles isolated from apoptotic blood cells and epithelial cells of morbidly obese patients what can be an evidence of an increased risk of thrombosis [19]. The increased level of TAT complexes directly confirmed of the blood hypercoagulability and they should be considered as a marker of thrombogenesis. Like our study, an increased level of thrombin-antithrombin complexes (TAT) in patients with morbid obesity was also noted by Thereaux et al. [20]. The extrinsic activation pathway is also regulated by TFPI directly inhibiting Xa and TF/VIIa complex. Reduced activity of TFPI is therefore associated with increased thrombogenic risk [21]. Antigen and activity of TFPI in our study did not change significantly both compared to surgery and reference group.

The aim of the present study was also to explore the impact of laparoscopic bariatric procedures on the blood clotting system and estimate the risk of thromboembolic complications after them. The hypercoagulable state after bariatric procedure was not induced by laparoscopic intervention itself because the examined parameters did not change significantly postoperatively [22].

A literature review did not reveal any publications of the impact of bariatric surgery on the coagulative effects in the postoperative period. An intention of the present study was to evaluate a risk of thromboembolic complications after bariatric laparoscopy in morbidly obese patients [23].

The number of available publications dealing with the effects of

bariatric surgery on haemostasis in morbidly obese patients is limited. Periasarny et al. reported positive changes in the blood clotting process such as a significant reduction in the amount of platelet-monocyte aggregates [24]. Minervino et al. in group of 58 morbidly obese patients found a significant postoperative reduction in the expressing of TF [25]. In another study Thereux et al. reported of postoperative reduction of thrombin formation in morbidly obese patients [20]. In morbidly obese patients treated with the bariatric procedure Kopp et al. found a significant decrease in TF levels but not in TFPI [17]. Similarly, to our study, Ay et al. reported decreased of TF activity [19]. Contrary to our results, after a laparoscopic bariatric procedure Rottenstreich et al. observed a hypercoagulability state induced by increased statistically significant generation of thrombin [15]. However, Thereaux et al. found a positive aspect of laparoscopic procedure by decreased generation of thrombin [16].

Postsurgical venous thromboembolism is presently based on solid principles and high-level scientific evidence. It depends on many factors such as a senility, degree of tissue traumatic during surgery and itself of the disease for example obesity [26]. Interesting examinations were conducting by Forfori et al. in patients with morbid obese who underwent surgical intervention. The authors did not find any essential changes in coagulable state after postoperatively. In their opinion the laparoscopic procedures performing on obese patients did not have an impact on their coagulation process [27]. We can also confirm above conclusions, based in our results especially on multivariate regression analysis where was established that no laparoscopic interventions but only BMI, history of deep vein thrombosis or history of pulmonary thromboembolism complications are independent factors of postoperative thrombosis.

The review of the literature reveals necessity of further studies on this subject. Therefore, these studies should be intensified in the search for other factors affecting haemostatic process of morbidly obese patients. Clarifying the problems of haemostasis in obese patients may resulting in reducing of thromboembolic complications and a sudden postoperative death.

Conclusion

The conclusion should be that bariatric procedures are not at an increased risk of postoperative thrombosis and they can be recommend in treatment of morbidly obese patients.

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