Bariatric surgery results in restoration of physiological plasma levels of pentraxine-3

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Abstract. Pentraxine-3 (PTX3) is a member of the humoral innate immune system and serves a role in protection against infections, inflammation control and matrix deposition. The aim of the present study was to measure the PTX3 levels in obese patients and its association with glycemic and lipid profiles, and to analyze the effects of weight loss provided by bariatric surgery in serum PTX3 levels. PTX3 was measured in 84 obese patients whom underwent bariatric surgery and 94 healthy controls. Lipid and glycemic profiles were determined using a clinical chemistry analyzer, and PTX3 levels were measured in patients prior to and following bariatric surgery using ELISA. PTX3 levels prior to surgery were significantly lower compared with the normal controls (median of 0.10 vs. 0.80 ng/ml; P<0.0001). Following surgery, the median weight loss was 33.1 kg, and the median PTX3 levels were significantly increased to 1.45 ng/ml compared with pre-surgery levels (P<0.001) and did not differ significantly from the control group levels (P=0.10). There were no correlations between PTX3 levels and total cholesterol, HDL and LDL, fasting glycemia, HbA1c and basal insulin levels. A significant positive correlation was observed between PTX3 levels and triglycerides levels in the post-operative period (ϱ=0.26, P=0.01). In conclusion, obese patients had lower levels of PTX3 compared with the control patients, and the levels were restored to physiological levels following bariatric surgery which may be associated with the weight loss.

Introduction

Pentraxin-3 (PTX3) is a long pentraxin identified in early 1990s that differs from short pentraxins, such as C reactive protein (CRP) and serum amyloid A, in gene organization, ligand binding abilities and the inducing stimuli (1). Similar to the other pentraxins, PTX3 is a member of the humoral innate immune system and serves a role in protection against infections (1,2), inflammation control and matrix deposition (3).

PTX3 and CRP are considered to be evolutionarily related antibodies (1). However, unlike CRP, which is induced by IL-6 and produced in the liver, PTX3 is formed locally by several cells and tissues following ligand binding to Toll-like receptors (TLR) and in response to proinflammatory signals, such as IL-1β and TNF-α (2).

There are conflicting results regarding the association between PTX3 atherogenic factors and obesity. Adipose cells produce PTX3 when stimulated by TNF-α, although the exact function it serves in this scenario is unknown (2). Zanetti *et al* (4) found that PTX3 serum levels are higher in individuals with metabolic syndrome and are negatively associated with HDL cholesterol and positively associated with plasma triglyceride levels. They also found an association between PTX3 concentrations and carotid intima thickness. Lee *et al* (5) described an inverse association between PTX3 levels and metabolic syndrome, being overweight/obese and parameters of dyslipidemia, suggesting a potential cardioprotective role of this marker. However, animal studies showed that PTX3 deficiency reduces metabolic inflammation and prevents weight gain in mice fed with a high fat diet (6).

Although PTX3 has been largely studied in association with obesity and dyslipidemia, few studies have examined changes in PTX3 levels following bariatric surgery. Santilli *et al* (7) studied PTX3 levels in 12 obese patients following gastric banding, and found that PTX3 levels were low in the preoperative period and they increased following the procedure, and PTX3 levels were inversely associated with platelet activation markers. Barazzoni *et al* (8) found that severely obese individuals had higher than normal PTX3 levels and following Roux-en-Y gastric bypass, the levels increased further.

In the present study, PTX3 levels in a sample of obese patients who underwent bariatric surgery were measured to analyze the variability in its levels in association with weight loss and changes in patients' metabolic profile.

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Patients and methods

Patients. The present study was a prospective study and was approved by the Committee of Ethics in Research, Sociedade Evangélica Beneficente de Curitiba (Curitiba, Brazil; approval no. 2.325.452). All participants provided signed informed consent for participation. A total of 84 obese patients undergoing bariatric surgery and 94 non-obese controls without any known disease, all aged >18 years, were recruited for the present study. Patients were classed as obese if they had a body mass index (BMI) ≥30 kg/m^2. This cohort was a convenience sample which includes all the patients who underwent bariatric surgery in a 1 year period, in two university hospitals from same geographic region and that agreed to participate in the study. In this sample 72/84 (85.7%) were females and 12/84 (14.2%) were males with a median age of 36 years (range, 19-63 years). Patients with chronic inflammatory diseases, a history of cancer, altered renal function and obesity secondary to endocrinopathies (such as Cushing's syndrome or hypothyroidism) were excluded. All patients underwent Roux-en-Y gastric bypass, and this was performed by the same surgical team following a multidisciplinary pre-operative evaluation by qualified clinicians in the fields of nutrition, endocrinology, cardiology and psychology. All patients underwent preoperative upper gastrointestinal endoscopy and abdominal ultrasound.

Data collection. Patients who underwent bariatric surgery were monitored for 60 days prior to the surgery and followed up in the post-operative period for 360 days. Epidemiological data regarding BMI, abdominal circumference, blood pressure, lipid profile (total cholesterol, HDL and LDL cholesterol, and triglycerides), fasting glycemia, hemoglobin A1c, basal insulin levels, uric acid, creatinine, albumin, blood cell count and transaminases were obtained at the same time as PTX3 measurements in the pre- and post-operative period.

Measurement of PTX3 levels. PTX3 levels were measured in plasma samples using a commercially available ELISA kit (XpressBio; cat. no. XPEH0263) with a detection range of 0.31-20 ng/ml and an inter-assay precision coefficient variation of <10%.

Statistical analysis. All statistical analyses were performed in GraphPad Prism version 6.01 (GraphPad Software, Inc.). Results were gathered in frequency and contingency tables. A Shapiro Wilk test was used to analyze data distribution. Comparison of nominal data was performed using a χ^2 test, comparisons of numerical data were performed using a Wilcoxon matched-pairs signed rank test or a Student's t-test based on the distribution of the data. Comparison of PTX3 levels between patients (pre and post-operative) and controls was performed using a Kruskal-Wallis test followed by a post-hoc Dunn's test. Correlation analyses of PTX3 with the other numerical variables were performed using Spearman's Rank Correlation tests. P<0.05 was considered to indicate a statistically significant difference.

Results

Characteristics of the recruited cohort. In the pre-operative period, 32/84 patients (38.1%) were diagnosed with dyslipidemia; 58/81 patients (71.6%) with hepatic steatosis; 41/84 patients (48.8%) with arterial hypertension; and 13/84 patients (15.5%) with diabetes mellitus. The post-operative evaluation was performed for between 106-375 days following surgery (mean ± standard deviation, 217±56.7 days) and the weight loss ranged from 14-72 kg with a median weight loss of 33.1 kg. The characteristics of the patients in the pre- and post-operative period are presented in Table I.

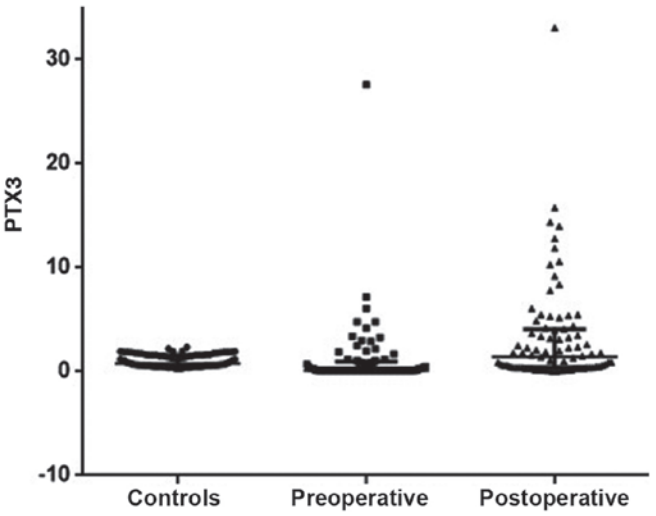

Figure 1. PTX3 serum levels in obese patients who underwent bariatric surgery and controls (n=84). The median PTX3 levels in the controls were 0.8 ng/ml (IQR, 0.5-1.6 ng/ml); in patients prior to surgery were 0.1 ng/ml (IQR, 0.1-0.97 ng/ml); and in patients following surgery were 1.45 ng/ml (IQR, 0.40-4.07 ng/ml). PTX3, pentraxin-3 levels; IQR, inter-quartile range.

PTX3 levels in the pre- and post-operative period. PTX3 levels in the control group and in the obese patients pre- and post-surgery are presented in Fig. 1. Comparison of PTX3 levels in pre- and post-operative patients and controls showed there was as significant difference (P<0.0001). The post-hoc Dunn's test showed that the PTX3 levels were significantly lower in the controls compared with the levels in the pre-operative patients, and the levels of PTX3 in the pre-operative patients were significantly lower compared with the levels in the post-operative patients (both P<0.05).

The variation in PTX3 values from pre- and post-surgery had a median value of 0.55 ng/ml; (inter-quartile range =0.12-2.97 ng/ml) and were not correlated with variations in BMI (ρ=-0.01; P=0.91) or the number of days following surgery (ρ=0.09; P=0.38).

No differences in PTX-3 serum concentrations were observed between males and females. In the pre-operative period, male patients had a median PTX3 level of 0.20 ng/ml (range, 0.10-1.77 ng/ml) and females had a median value of 0.10 ng/ml (range, 0.10-0.90 ng/ml) (P=0.45). In the post-operative period, the median value in males was 0.45 ng/ml (range, 0.20-3.50) and in females it was 1.55 ng/ml (range, 0.40-4.15) (P=0.18).

Correlation analysis of the PTX3 levels prior to surgery with clinical and metabolic variables did not show any statistical significance. Correlation analysis of the PTX3 levels following surgery with clinical and metabolic variables showed that there was significant positive correlation with

Table I. Primary characteristics of the patients who underwent bariatric surgery.

Variables	Before surgery	After surgery	P-value
BMI (kg/m^2)			<0.0001[d]
Range	35.1-64.8	22.4-44.5	
Median (IQR)	44.6 (41.4-48.1)	31.0 (28.4-34.3)	
Systolic BP, mm Hg			<0.0001[d]
Range	90-200	90-170	
Median (IQR)	125 (110-140)	120 (110-120)	
Diastolic BP, mm Hg			<0.0001[d]
Range	60-110	50-100	
Median (IQR)	80 (70-90)	70 (70-80)	
Abdominal circumference, cm			<0.0001[d]
Range	102-176	73-141	
Median (IQR)	126 (118-137)	100 (93-110)	
Total cholesterol, mg/dl			<0.0001[d]
Range	120.0-291.0	116.0-234.0	
Median (IQR)	191.7 (167.4-222.0)	167 (139-189)	
LDL cholesterol, mg/dl			<0.0001[d]
Range	60-184	44-146	
Mean ± SD	118.6±29.2	99.9±24.1	
HDL cholesterol, mg/dl			0.96
Range	29.2-81.0	28.7 - 79.0	
Median (IQR)	45.3 (36.0-53.0)	46.0 (39.0-52.0)	
Triglycerides, mg/dl			<0.0001[d]
Range	68-462	38-343	
Median (IQR)	135.3 (101.8-178.8)	94 (72.5-134.0)	
Fasting glucose, mg/dl			0.0002[c]
Range	66-408	60-137	
Median (IQR)	91 (82-103)	87.5 (79.2-92.0)	
Hemoglobin A1c, %			<0.0001[d]
Range	4.7-9.9	4.0-8.1	
Median (IQR)	5.4 (5.2-5.9)	5.2 (5.0-5.6)	
Basal insulin, mIU/l			<0.0001[d]
Range	3.0-168.7	1.6-42.4	
Median (IQR)	15.6 (8.3-27.8)	6.8 (4.5-12.1)	
Uric acid, mg/dl			<0.0001[d]
Range	2.0-9.3	1.9-7.2	
Mean ± SD	4.8±1.45	4.3±1.20	
Ferritin, ng/ml			0.10
Range	7-1042	9.8-697.0	
Median (IQR)	165.0 (55.3-259.5)	128.0 (73.0-243.0)	
Albumin, g/l			0.02[a]
Range	3.4-4.8	3.1-5.3	
Median (IQR)	4.0 (3. 8-4.3)	4.1 (4.0-5.3)	
Oxalacetic transaminase, U/l			0.58
Range	9-90	9-52	
Median (IQR)	22.5 (18.0-33.0)	25 (18-31)	
Pyruvate transaminase, U/l			0.06
Range	6-145	9-79	
Median (IQR)	26.0 (17.0-39.2)	24 (16-37)	
Creatinine, mg/dl			0.20
Range	0.5-1.2	0.5-1.2	
Median (IQR)	0.8 (0.7-0.9)	0.8 (0.7-0.9)	

Table I. Continued.

Variables	Before surgery	After surgery	P-value
Hemoglobin, g/dl			0.14
Range	11.4-16.6	10.6-15.9	
Median (IQR)	13.1 (12.5-14.0)	12.9 (12.5-13.6)	
Hematocrit, %			0.059
Range	31.5-49.7	32.5-47.6	
Mean ± SD	39.9±3.41	39.3±3.16	
Platelets, n/mm^3			0.19
Range	127,000-474,000	138,000-465,000	
Median (IQR)	241,500 (209,250-291,000)	233,000 (195,200-288,250)	
Vitamin D, ng/ml			0.001[b]
Range	6.8-47	9.7-52.0	
Median (IQR)	25.5 (18.6-29.9)	28.5 (24.2-33.7)	

[a]P<0.05, [b]P<0.01, [c]P<0.001, [d]P<0.0001. IQR, inter-quartile range; SD, standard deviation; BMI, body mass index; BP, blood pressure.

Table II. Correlation analysis of variability of values prior to and following bariatric surgery with the variability in pentraxin-3 levels.

Variables	Spearman ρ	95% confidence interval	P-value
Δ Body mass index	-0.04	-0.26-0.17	0.68
Δ Total cholesterol	-0.04	-0.26-0.18	0.70
Δ HDL cholesterol	0.08	-0.14-0.30	0.47
Δ Triglycerides	-0.06	-0.29-0.16	0.55
Δ Basal insulin	0.07	-0.20-0.34	0.59
Δ Fasting glycemia	0.008	-0.21-0.23	0.53
Δ Hemoglobin A1c	0.007	-0.20-0.34	0.59
Δ Uric acid	-0.18	-0.39-0.05	0.12

Δ, difference in.

triglyceride levels (although this correlation was modest; ρ=0.26; 95% CI, 0.03-0.46; P=0.01). Detailed results of the correlation analyses between pre- and post-surgery PTX3 levels with other variables are presented in Table II.

Discussion

The results of the present study showed that obese patients have lower levels of PTX3 compared with non-obese patients and that bariatric surgery results in restoration of physiological levels. These results are in agreement with previous studies from Ogawa *et al* (9) and Osorio-Conles *et al* (10), who both found an inverse association between the serum blood levels of PTX3 and BMI. In addition, PTX3 serum levels are increased in obese patients who underwent dietary intervention (11) and gastric banding (7).

There was no association between PTX3 levels and the lipid profile or the glycemic controls; however, the elevation of this biomarker itself is of interest for patients undergoing bariatric surgery as it has been shown that PTX3 may exert a protective role on the cardiovasculature (12). Animal studies of PTX3 null mice demonstrated that they develop severe inflammatory changes in the vascular walls, with an increased number of macrophages in atherosclerotic plaques, suggesting that PTX3 may exert a regulatory function in vascular associated inflammation (12). In an experimental ischemia-reperfusion model of myocardial infarction, PTX3 deficient animals showed significantly larger infarcts compared with the wild-type controls, suggesting that PTX3 serves a role in myocardial damage and repair (13). PTX3 deficient animals had higher deposition of C3 (complement system) in the damaged tissue, thus it is possible that the protective function of PTX3 may transpire through prevention of tissue damage by excessive complement deposition (13). PTX3 inhibits activation of the classic complement pathway by preventing an interaction between immunoglobulins and C1q (14), and inhibits the alternate pathway by controlling the deposition of H factor in apoptotic cells (15).

Norata *et al* (16) showed that HDL-cholesterol is capable of inducing the expression of PTX3 mRNA in vascular endothelial cells. They suggested that the protective effect of HDL on atherosclerosis may partly be due to its modulation of PTX3 secretion.

Obesity is a low-grade inflammatory disease and a significant risk factor of cardiovascular morbidity (17). A study on PTX3 gene expression in cultured adipocytes found that PTX3 is upregulated locally, and that the production of this biomarker is higher in visceral adipose tissue compared with subcutaneous fat (10). However, in the same study, the blood levels of PTX3 were inversely associated with obesity and thus the authors hypothesized that local production of PXT3 regulates the equilibrium between an inflammatory and anti-inflammatory response (10). Therefore, if PTX3 exerts a protective effect against metabolic syndrome, lowering blood PTX3 levels in obese patients may lead to a reduction in the inflammatory process resulting from increased fat mass (11).

There was no association between PTX3 levels and insulin levels, glycemic controls or any of the lipid profile fractions assessed except for triglycerides following surgery. Contrasting results regarding the association between PTX3 levels and

triglycerides have been reported. Zanetti *et al* (4) found a positive correlation between plasma triglyceride and PTX3 levels, whereas a negative association was observed by Lee *et al* (5) and Yamasaki *et al* (18). A possible explanation for the discrepant results may be due to small sizes in each study and the use of patients with a specific disease (11). In the present study, a modest but significant positive correlation was observed between PTX3 and triglycerides levels in the post-operative period.

The present study has some limitations: The PTX3 measurements were taken at different intervals following surgery and there was a relatively lower number of males in the experimental cohort (14.3%). Additional studies, with a higher proportion of male patients and fixed intervals of PTX3 measurement will increase the reliability of the results and allow for stratification by sex to remove this as a potential confounding factor, thus clarifying the results further. Nevertheless, the present study does show that bariatric surgery restores PTX3 levels to physiological levels, demonstrating the beneficial effect of this type of surgery on cardiovascular risk.

In conclusion, the study showed that bariatric surgery restores PTX3 levels to physiological levels. Additional studies are required to understand the value increased PTX3 levels in obese patients on the prevention of cardiovascular.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

AFT, RN, PANN and TS designed and performed the experiments. SIM, AGC and JSCG collected the patients' data and serum samples. AFT, RN and TS organized and analyzed data. All authors were involved in writing the paper and approved the final version of the manuscript.

Ethics approval and consent to participate

The present study was a prospective study and was approved by the Committee of Ethics in Research, Sociedade Evangélica Beneficente de Curitiba (Curitiba, Brazil; approval no. 2.325.452). All participants provided signed informed consent for participation.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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