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Pre-operative and post-operative changes in CRP and other biomarkers sensitive to inflammatory status in patients with severe obesity undergoing laparoscopic sleeve gastrectomy

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ABSTRACT

Introduction: C-reactive protein (CRP) is often elevated in patients living with severe obesity (BMI ≥ 35 kg/m^2). However, there is limited information on how CRP, and other inflammation responsive biomarkers, change in response to weight loss following laparoscopic sleeve gastrectomy (LSG). We studied how CRP, ferritin and albumin change following LSG surgery in relation to obesity, metabolic syndrome (MetS) ATPIII risk components and diabetes mellitus (DM).

Methods: Laboratory parameters (including CRP) were examined in 197 patients prior to LSG, and at 6, 12, 18 and 24 months. Changes in laboratory parameters, and laboratory investigations, were also examined in a 125 patient subgroup at both pre-LSG and at the 12 month follow-up visit.

Results: All patients had BMI ≥ 35 kg/m^2. CRP levels positively correlated with BMI ($r = 0.171$, $p = 0.016$) and alkaline phosphatase (ALP; $r = 0.309$; $P < 0.001$), but negatively correlated with alanine aminotransferase (ALT; $r = -0.260$; $P < 0.001$) and albumin ($r = -0.358$; $P < 0.001$). LSG significantly reduced CRP and ferritin, which were maintained for at least 24 months. At 12 months post-LSG there was a significant decrease in weight (kgs) ($p < 0.001$), CRP ($p < 0.001$), ferritin ($p = 0.004$), and various MetS risk components ($p < 0.001$) but not albumin ($p = 0.057$). Changes in CRP also correlated with changes in weight ($r = 0.233$, $p = 0.018$) and ALP ($r = 0.208$, $p = 0.034$) but not albumin ($r = -0.186$, $p = 0.058$) or ferritin ($r = 0.160$, $p = 0.113$) after LSG.

Conclusion: The negative correlation between CRP and albumin levels in obesity may indicate a low grade inflammatory process affecting both. LSG related weight loss decreased CRP and ferritin, likely explained by improvement in inflammatory status.

1. Introduction

Obesity results from chronic and excessive accumulation of adipose tissue due to chronic energy imbalance between intake and expenditure, and affects about 13% of the world's adult population [1]. The prevalence of obesity is higher in Canada affecting about 1 in 5 adults [2], and the province of Newfoundland and Labrador has the highest level in Canada at 30.4% [3]. Obesity is often measured as body mass index (BMI). Class II (BMI 35 to 39.99 kg/m^2) and Class III (BMI ≥ 40 kg/m^2), often referred to as severe obesity, is a major risk factor for obesity related co-morbidities like type II diabetes mellitus (Type II DM), cardiovascular disease and stroke, hypertension, asthma, and certain types of cancer. A number of longitudinal studies also link obesity with insulin resistance, a key determinant of the metabolic syndrome (MetS), forerunner to Type II DM, and a high risk condition for cardiovascular disease. The pathogenic mechanism linking obesity with insulin resistance conditions remains an area of active investigation, and some suggest that the low-grade sub-clinical chronic inflammatory process that accompanies obesity may play a causative role in the development of insulin resistance [4,5]. Hence, inflammation is

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an important determinant of the pathological consequences of severe obesity [6] including MetS and Type II DM.

The acute phase response describes the increase in blood plasma proteins in response to inflammation and tissue damage. These acute phase reactants respond to chronically increased levels of pro-inflammatory cytokines released through low-grade chronic activation of the innate immune system by adipose tissue remodeling, adipocyte hypertrophy, macrophage infiltration, and angiogenesis. C-reactive protein (CRP) has emerged as the main acute phase reactant inflammatory marker in clinical practice and can rise over 100-fold during inflammation. Many studies have demonstrated the positive association between CRP with various measures of obesity, obesity related disease, and cardiovascular risk [7]. Ferritin, an iron binding protein present in most tissues, is a key regulator of iron homeostasis, and a longstanding biomarker for depletion of body stores of iron [8]. During acute and chronic inflammatory processes ferritin may rise several times greater than baseline levels [9,10]. Elevated levels of serum ferritin is also associated with Type II DM, MetS [11], and central obesity [12,13]. Albumin is both a nutritional biomarker, an inflammatory responsive protein, and the major determinant of oncotic pressure. Inflammation simultaneously decreases albumin synthesis and increases albumin breakdown. Chronic conditions with inflammatory components lead to lower albumin concentration, but it remains unclear if low grade inflammation found in obesity significantly affects serum albumin concentrations [14–16].

Laparoscopic sleeve gastrectomy (LSG), has recently emerged as a stand-alone therapeutic intervention for the treatment of severe obesity which brings about significant post-surgery weight loss [17,18]. Previous studies have shown LSG to also induce early and sustained reductions in CRP levels for up to 12 months [19]. In Newfoundland and Labrador (NL), one in three adults is living with obesity (~30%) and an estimated 8% (approximately 29,000 individuals) are living with severe obesity and are potentially eligible for surgery. Eastern Health, the largest health authority in the province, established a multi-disciplinary bariatric surgery program in 2011. LSG, the preferred procedure (representing 98% of bariatric surgeries performed), is offered as a treatment to adults living with severe obesity. The purpose of this study is to assess the inflammatory status of LSG eligible patients using CRP, and to examine the relationship of CRP with other metabolic risk factors related to obesity, insulin-resistance, and MetS. This study also examines CRP, ferritin, and albumin levels at 6, 12, 18 and 24 months post-operatively to determine how changes potentially relate to the inflammatory state and metabolic risk factors.

2. Methods

This study is part of a prospective bariatric surgery cohort (BaSco) study examining patients before and for 24 months after LSG. The detailed study protocol has been previously published [20]. Patient eligibility for surgery and hence the study participation was based on previously published guidelines [21], and surgery was conducted at the Health Sciences Centre located in St. John's, NL as previously described [22]. All elements of this study involved patients undergoing surgery from May 2011 to May 2014 and was conducted in accordance with the requirements of the provincial Health Research Ethics Authority from which ethics approval for this work was granted. All patients provided informed consent to take part in the study.

2.1. Laboratory analyses

Blood samples were collected 1 to 2 days prior to surgery to serve as baseline values, and at approximately 6, 12, 18, and 24 months afterward. All blood samples were drawn after a 12 h fast. All initial samples were processed in accordance with clinical laboratory protocols at the clinical laboratories located at Health Science Centre. During follow-up, samples were analyzed at local clinical laboratories using methodologies described below. Briefly, insulin and ferritin analyses were done on Architect I series immunoassay systems (Abbott Diagnostics). Hemoglobin A1c (HbA1c) was analyzed using dedicated high pressure liquid chromatography instrumentation (G8 HPLC analyzer; Tosoh). Other laboratory tests including alanine amino transferase (ALT), aspartate amino transferase (AST), gamma glutamyl transferase (GGT), total bilirubin, total cholesterol, HDL-cholesterol (HDL-C), triglycerides, glucose, albumin, and CRP were done on Architect C series clinical chemistry analyzers (Abbott Diagnostics). The CRP method was calibrated for high sensitivity CRP determination. Calculated parameters included LDL-Cholesterol and was determined by the Friedwald Equation, and non-HDL-Cholesterol, determined as the difference between measured total cholesterol and HDL-Cholesterol. The eGFR was calculated based on the modification of diet in renal disease (MDRD) equation for serum creatinine standardized to isotope dilution mass spectrometry method. The 12 month absolute weight loss (AWL) was determined as the pre-LSG body weight (kg) subtracting the body weight at 12 month post-LSG follow-up visit. The proportion of absolute weight loss (PAWL) was determined as the AWL divided into the pre-LSG body weight. For some analyses the proportion of values above the upper reference limit (URL) or below the lower reference limit (LRL) were used to identify abnormality.

2.2. Statistical analyses

All data analysis were performed using the Minitab version 17.2.1 statistical software. All continuous data was tested for normality, prior to application of other statistical tests, by applying the Kolmogorov-Smirnov test. All continuous variables that were normally distributed were summarized and expressed as mean ± standard deviation, and non-normally distributed variables were expressed as median and range (minimum and maximum). Assessment for statistically significant differences between groups was determined by the Student *t*-test and ANOVA for normally distributed variables, and by Mann-Whitney U-test and Kruskal-Wallis test for non-normally distributed variables. The post-hoc Tukey's multiple comparison test was used to determine different means among groups after ANOVA. The correlation between different variables were determined by the Spearman's Rank test, because of the non-normality of most data. Differences between all data expressed as proportions were determined by Fishers Exact test. Statistically significant differences are defined by $p < 0.05$.

3. Results

Baseline characteristics of 197 patients were studied prior to LSG (Table 1). They include anthropomorphic measurements, blood pressure, laboratory parameters such as lipids, indices of glycemia, renal damage, liver function, and biomarkers known to be responsive to inflammatory states including CRP. All subjects were severely obese with a median BMI of 48.6 kg/m^2 (range 35.2 to 67.2 kg/m^2). Results were compared across patient subgroups based on obesity only (1 and 2 MetS risk factors; 16.8%), or having MetS without DM (40.1%), or DM (43.1%). There was a statistically significant difference in all lipid parameters (total cholesterol, triglycerides, HDL-Cholesterol, calculated LDL-Cholesterol, non-HDL cholesterol), indices of glycemia (fasting glucose, HbA1c, fasting insulin levels, and HOMA-IR), systolic and diastolic blood pressure, and for several other biochemical parameters including serum ferritin, ALT, ACR, and GGT levels among the patient subgroups. Ferritin levels were higher in subjects with MetS or DM than in the obesity-only subgroup. However, there were no significant difference with respect to any of the anthropomorphic measurements, CRP, albumin, ALP, or total bilirubin across groups. All patients had either Class II (n = 18) or Class III (n = 177) obesity based on BMI. There were no significance differences in CRP (p = 0.687), ferritin (p = 0.721), or albumin (p = 0.505) levels between groups based on BMI class (data not shown).