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ORIGINAL RESEARCH

The Evaluation of Serum Endocan, Interleukin-6, and CRP Levels Following Sleeve Gastrectomy

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Background: The excessive accumulation of fat tissue in obesity is the source of chronic low-level inflammation and causes future dysmetabolic and cardiovascular disorders. Removal of this excessive fat tissue with the aid of bariatric surgery (BS) techniques, such as sleeve gastrectomy, may reverse adverse inflammatory outcomes. The aim of this study is to investigate the impact of sleeve gastrectomy on inflammatory markers, specifically endocan, IL-6, and CRP, in individuals with obesity.

Methods: Thirty-two patients with class 3 obesity and class 2 obesity + comorbidities were enrolled in the study. Clinical characteristics including age, comorbidity, body mass index (BMI), waist, and hip circumferences of the participants were noted before and 3 months after sleeve gastrectomy. Blood samples were collected during those periods to assess biochemical features such as serum endocan, interleukin-6 (IL-6), C-reactive peptide, fasting insulin, glycosylated hemoglobin A1c levels, and lipid panel. A statistical package program was used for the analysis of those parameters, and $p<0.05$ was accepted as significant at a 95.0% confidence interval.

Results: BMI reduced from 43.55±6.78 to 36.16±6.14 kg/m2 within 3 months following BS ($p<0.001$). Preoperative serum endocan, IL-6, and CRP levels were correlated with BMI, and in line with BMI reduction, their serum levels decreased after BS ($p<0.05$). HOMA-IR also reduced after BS, and both in the pre and post-BS periods correlated with BMI, IL-6, endocan, and CRP levels ($p<0.05$). The mean total body weight loss was 20.4% within 3 months post-BS.

Conclusion: BS techniques are effective in weight loss and reversing the inflammatory processes caused by obesity. Serum endocan, IL-6, and CRP levels are promising markers for describing obesity-related inflammation and objectively checking the alleviation of inflammation following BS.

Keywords: bariatric surgery, endocan, interleukin-6, sleeve gastrectomy, weight loss

Introduction

Obesity, by definition, is the accumulation of excessive fat tissue in the body. The accumulated fat tissue in obesity is also the source of dysmetabolic and chronic inflammatory processes, which are crucial disease-related complications.[1–3] Furthermore, as the obesity stage progresses, the adverse metabolic effects become more frequent and severe.[4,5]

Bariatric surgery (BS), also known as metabolic surgery, is the most preferred treatment option for a group of patients with obesity, including the following categories: 1) body mass index (BMI) >35 kg/m2, regardless of the presence, absence, or severity of co-morbidities; 2) patients with T2D and BMI >30 kg/m2; 3) individuals with a BMI of 30–34.9 kg/m2 who do not achieve substantial or durable weight loss or improvement in co-morbidities using nonsurgical methods.[6] BS can reverse the adverse impact of type 2 diabetes mellitus (T2DM), hypertension, dyslipidemia, and non-alcoholic fatty liver disease in individuals with obesity, and the benefits of BS seem to go beyond weight reduction.[7,8]

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Bariatric surgery is associated with a decline in inflammation. This is shown by a decrease in some inflammatory markers, such as monocyte chemoattractant protein-1, expression of toll-like receptors (TLR-2 and TLR-4; the receptors for Gram-positive bacterial residues and endotoxin), intranuclear binding of nuclear factor kappa-β, the plasma concentration of matrix metallopeptidase-9 (MMP-9), c-reactive protein (CRP), and the indicator of activated monocytes. Furthermore, the expression of CD14 is increased after BS.[9] Previous studies have demonstrated that improvement in inflammation and insulin sensitivity following BS commonly occurs immediately within the postoperative 1 month and remains stable for 12 months.[10,11] Furthermore, following BS, increased insulin sensitivity is associated with a reduction in inflammation markers, especially in patients with T2DM.[12–14]

Endocan, also known as endothelial-specific molecule-1 (ESM1), is a protein encoded by the ESM1 gene in humans and inhibits leukocyte adhesion and migration through the endothelium.[15,16] It is uncertain whether endocan levels change with weight reduction in obesity. Interleukin-6 plays a key role at the site of inflammation by secreting from local macrophages, stimulating T and B-lymphocytes, and finally causing the transition from acute to chronic inflammation.[11,17] Both adipocytes and adipose tissue macrophages can produce IL-6, and BS can reduce serum IL-6 levels.[11,17,18]

This study aims to investigate the changes in inflammation markers (endocan, IL-6, and CRP) in individuals with BMI ≥35 kg/m2 following BS at 3 months.

Materials and Methods

Case Selection

This prospective self-controlled study was conducted in 2022 at Medicana International Ankara Hospital, including thirty-two patients with BMI ≥35 kg/m2 who underwent sleeve gastrectomy. The study aimed to compare the individuals' preoperative and 3-month postoperative metabolic and inflammation parameters. Before starting the study, the targeted sample size was calculated as 45, considering an effect size of 0.50, α error probability of 0.05, and 1-β error probability of 0.95 (using GPower 3.1.9.7). However, during the data acquisition, when we reached 32 participants, we calculated Cohen's D as the effect size and found it to be 0.77 for endocan and 0.61 for interleukin-6. Lastly, given the effect sizes of those parameters, 20 individuals were found sufficient for the assessment of endocan, and 31 individuals were found sufficient for the assessment of interleukin-6, using GPower for evaluation.

Exclusion Criteria

Individuals with acute infections, a history of cardiac disease, and long-standing type-2 diabetes mellitus (T2D) requiring polypharmacy such as oral antidiabetic or antilipidemic medications were excluded. Additionally, individuals <18 and >75 years old were not considered for metabolic surgery in our center. All recipients underwent surgery following at least 3 months of a failed weight loss program, including a strict low-calorie diet and adjuvant pharmacological agents.

Ethics Approval

The study protocol was approved by the Medicana International Ankara Hospital Ethics Committee with the number BSH 2022/19. The patients were informed about the study, and written consent forms were obtained. The principles of the Declaration of Helsinki were followed in this study.

Obesity is defined as BMI ≥30 kg/m^2 and staged as; Class 1; ≥ 30 kg/m^2 and <34,99 kg/m^2, Class 2; 35≥ kg/m^2 and <40,0 kg/m^2, and Class 3; ≥40 kg/m^2 according to WHO guidelines (https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight published June 9, 2021. Accessed: June 25, 2023).

Laboratory Assessment

Serum glycated hemoglobin A1c (HbA1c), fasting glucose, uric acid, complete blood count, alanine aminotransferase, albumin, lipid profile, C-reactive protein (CRP), ferritin, insulin, endocan, and IL-6 levels were studied. Homeostatic model assessment insulin resistance (HOMA-IR) was calculated. Blood samples were taken in the morning after fasting for at least 12 hours. Subsequently, the samples were left to clot for 30 minutes to obtain sera and then centrifuged at room temperature for 5 minutes at 4000 revolutions per minute. Serum endocan levels were analyzed using an enzyme-linked

immunosorbent commercial assay (Human ESM1 ELISA Kit, Elabscience E-EL-H1557) with a microplate reader (BIO-TEK EL X 800, Auto strip washer; BIO TEK EL X 50). Serum interleukin-6 levels were analyzed using an Electrochemiluminescence immunoassay (ECLIA) assay (Human Elecsys IL-6 Kit, Roche 05109442190, by Roche 411 Roche Diagnostics GmbH, Mannheim, Germany). The immunoturbidimetric method was used for the determination of HbA1c in whole blood samples (Roche Cobas c501 chemistry analyzer, Roche Diagnostics GmbH, Mannheim, Germany). Serum glucose and lipid parameters (total cholesterol [TC], triglycerides [TG], low-density lipoprotein cholesterol [LDL-C], and high-density lipoprotein cholesterol [HDL-C]) were measured spectrophotometrically, using the same autoanalyzer as for HbA1c. Serum hsCRP levels were obtained by nephelometric assay (Behring Nephelometer Analyzer, Marburg, Germany).

Anthropometric Measurements

Body mass index (calculated as weight divided by height squared [kg/m2]), waist circumference, and hip circumference (in centimeters) were measured before and after BS.

Statistical Analysis

Data analysis was performed using a statistical package program (SPSS for Windows version 17.0, IBM Corp., Armonk, NY, USA). The distribution of continuous variables was tested using the Kolmogorov–Smirnov test. Descriptive parameters were presented as mean ± standard deviation for parametric variables and median values (minimum and maximum) for nonparametric variables. Categorical variables were compared using the Chi-Square test. Paired-samples *t*-test and Wilcoxon Two-related Samples test were used to compare variables before and after surgery. A regression model was applied to estimate the potential independent prediction of factors on endocan and IL-6 levels. Parametric Pearson's and nonparametric Spearman correlation analyses were performed to demonstrate the correlation between variables. Two-tailed p-values <0.05 were considered statistically significant with a 95% confidence interval.

Results

A total of 32 patients with BMI ≥ 35 kg/m2, with a mean age of 37.40±10.70, were evaluated. BMI reduced from 43.55±6.78 to 36.16±6.14 (a reduction rate of 17.06%) within 3 months following sleeve gastrectomy (p<0.001). The BMI reduction rate after BS was higher in females (pre-BS: 43.17±6.52 and post-BS: 35.47±5.50, a reduction rate of 17.83%) compared to males (pre-BS: 44.39±7.60 and post-BS: 37.68±7.42, a reduction rate of 15.38%), (p=0.05). Among the participants, 34.4% had Class 2 obesity and 65.6% had Class 3 obesity. The BMI reduction rates were 18.24% in Class 2 and 16.45% in Class 3 following BS. Fourteen individuals with Class 3 obesity (66.6%) transitioned to Class 2 following BS, but the patients who remained in Class 3 also experienced significant weight loss compared to their preoperative weight (pre-BS: 53.46±4.40 and post-BS: 45.46±3.44, a reduction rate of 14.83%, and p<0.001). The demographic and laboratory features of the participants are presented in Table 1 and Table 2. Serum endocan, IL-6, CRP, fasting insulin, total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), and alanine aminotransferase (ALT) levels decreased, while high-density lipoprotein cholesterol (HDL-C) levels increased after BS (Table 2). The correlations between these parameters pre-BS and post-BS are provided in Table 3. HOMA-IR and HbA1c levels reduced after BS; however, no correlation between BMI and HOMA-IR or HbA1c was found (Table 1 and Table 2). This result may be attributed to 4 out of 5 diabetic individuals being in the Class 2 group.

The potential confounding factors were investigated in a univariate regression model. Sex, smoking status, and the presence of comorbidities (DM, HT, IR, etc.) were found to have no impact on pre-BS endocan levels (p=0.374, p=0.376, and p=0.238, respectively). The same model was applied for IL-6 and CRP and found no impact on their levels (p>0.05). The impact of sex, smoking status, and comorbidities was also re-analyzed post-BS and found to have no impact on serum endocan, IL-6, and CRP levels in this cohort (p>0.05). Age had no correlation with serum endocan levels in the pre-BS and post-BS periods (p=0.215 and p=0.886, respectively).

We did not study the predictivity and sensitivity tests by using ROC analysis for endocan, IL-6, and CRP, since endocan levels decreased in all individuals, IL-6 levels decreased in all except one case, and CRP levels decreased in all except 3 cases following BS. So, the current study clearly indicates those inflammatory markers will alleviate after BS.

Table 1 The Demographical and Laboratory Features of Individuals with BMI ≥35 kg/m^2

Age, Years	37.40±10.70
Sex, male/female, n	10/22
Smoker, yes/no	17/15
OSAS, yes/no	1/31
Comorbidity; n	
• No	11
• DM	5
• HT	6
• IR	1
• Other	9

Abbreviations: BMI, body mass index; BS, bariatric surgery; OSAS, obstructive sleep apnea syndrome; DM, diabetes mellitus; HT; hypertension; IR; insulin resistance.

Table 2 The Comparison of Pre and Postsurgical Metabolic and Inflammatory Parameters

	Before BS	After BS (3 Months)	P value	Reference Values
BMI, kg/m2	43.55±6.78	36.16±6.14	<0.001	
Obesity, n • Class 1 • Class 2 • Class 3	 – 11 21	 15 (+2 Overweight) 8 7		
HgbA1c, %	6.66±1.72	5.90±1.13	<0.001	<5.6%
Fasting insulin, mIU/L	31.16± 15.21	18.20±8.32	<0.001	2.6–24.9
HOMA -IR	5.76±1.96	2.99±0.89	<0.001	<1.9
IL-6, pg/mL	15.28±8.69	5.01±2.90	<0.001	NA*
Endocan, ng/mL	392.93±57.96	259.93±51.37	<0.001	NA*
Waist circle, cm	130.18±17.11	117.34±14.47	<0.001	<89 (female) <94 (male)
Hip circle, cm	139.31±16.87	128.75±16.15	<0.001	
CRP, mg/L	7.211±5.14	4.39±3.49	0.006	0–5.0
Total cholesterol, mg/dl	227.78±45.88	192.07±26.82	<0.001	<200
LDL cholesterol, mg/dl	133.45±30.76	111.62±26.41	<0.001	<130
HDL cholesterol, mg/dl	44.00±8.32	51.55±9.90	<0.001	>40
Triglyceride, mg/dl	234.72±116.318	161.62±57.34	<0.001	<150
ALT, U/L	33.50±14.66	29.20±9.46	0.008	4–30

Notes: *There is no control group to establish reference L-6 and endocan values from pooled data in this study. So, the reference range for IL-6 and endocan is not available.

Abbreviations: BMI, body mass index; BS, bariatric surgery; HgbA1c, hemoglobin A1c; HOMA-IR, homeostatic model assessment insulin resistance; IL-6, interleukin-6; CRP, c-reactive protein; LDL, low-density lipoprotein; HDL, high-density lipoprotein; ALT, alanine transaminase.

Table 3 The Correlation Between the Laboratory Parameters and Pre- and Post-BS

	Pre-BS BMI		Post-BS BMI	
	P value	R^2	P value	R^2
Endocan, ng/mL	0.007	0.221	<0.001	0.497
IL-6, pg/mL	<0.001	0.405	<0.001	0.528
HgbA1c, %	0.606	−0.009	0.685	−0.006
HOMA-IR	0.068	0.215	0.218	0.080
Fasting insulin, mIU/L	<0.001	0.422	<0.001	0.487
CRP, mg/dl	0.048	0.142	<0.001	0.353
Waist circle, cm	<0.001	0.553	<0.001	0.362
Hip circle, cm	<0.001	0.529	<0.001	0.425
Total cholesterol, mg/dl	0.039	0.123	0.031	0.147
LDL cholesterol, mg/dl	<0.001	0.438	0.006	0.226
HDL cholesterol, mg/dl	0.012	−0.193	0.001	−0.179
Triglyceride, mg/dl	0.002	0.277	<0.001	0.455
ALT, U/L	<0.001	0.555	<0.001	0.443

Abbreviations: BMI, body mass index; BS, bariatric surgery; HgbA1c, hemoglobin A1c; HOMA-IR, homeostatic model assessment insulin resistance; IL-6, interleukin-6; CRP, c-reactive protein; LDL, low-density lipoprotein; HDL, high-density lipoprotein; ALT, alanine transaminase.

Discussion

Obesity has many cardiometabolic adverse outcomes which arise from a chronic inflammatory process. The description of the inflammatory status is as important as the diagnosis of obesity since they may force the clinicians and the patient to more aggressive therapies such as BS. This study indicates sleeve gastrectomy is effective in lowering the high levels of the inflammatory markers endocan, IL-6, and CRP. Additionally, this is the first longitudinal study demonstrating the impact of BS on endocan levels.

Morbid obesity is linked to severe comorbidities like T2DM, hypertension, atherosclerosis, sleep apnea, and cardiovascular diseases. While lifestyle changes are crucial for treating obesity, they may not yield significant clinical benefits for most individuals, particularly those with morbid obesity. In such cases, surgical interventions are necessary when obesity is accompanied by long-standing comorbidities.

Following BS, it is expected that inflammation and related mediators gradually decline. Schernthaner et al[19,20] reported significant decreases in monocyte chemoattractant protein-1 (MCP-1), CRP, and circulating IL-18 levels after BS. These atherosclerosis-related parameters were also found to be associated with improvements in HOMA-IR and glucose levels following BS.[21,22] Monte et al[9] reported improvements in toll-like receptor-2 and 4 activities in mononuclear cells, plasma concentration of matrix metallopeptidase-9, CRP, and intranuclear binding of nuclear factor kappa B in patients with obesity 6 months after BS. CRP reduction is particularly evident within 1 month after BS, especially in insulin-sensitive patients.[12] Another study showed a significant decrease in CRP at 3 months and improvements in serum-tartrate-resistant acid phosphatase 5a (TRCP 5a) and IL-6 at 6 months postoperatively.[13] However, the rate of reduction may vary among patients, especially in those with diabetes. Diabetic patients with obesity, who have a low-grade chronic inflammation associated with hyperglycemia and elevated free fatty acid concentration, may require more time to experience clear clinical benefits.[21,22] A study by Lasselin et al[23] demonstrated that a higher inflammatory state of adipose tissue, indicated by serum TNF-a and IL-6 levels, could predict a lower reduction in BMI after surgery. In this study, the decline in CRP and IL-6 levels following BS is

consistent with previous studies. Furthermore, serum levels of CRP and IL-6 showed strong correlations with BMI in both the pre- and post-surgical periods.

Endocan is a novel proteoglycan that is secreted by vascular endothelium and plays a role in various cellular processes, including cell differentiation, migration, and adhesion. Recent studies have highlighted the involvement of endocan in inflammation.[24,25] During acute infection, endocan inhibits the migration and homing of leukocytes by binding to lymphocyte function-associated antigen-1 (LFA-1), thereby interfering with the interaction between LFA-1 and endothelial intercellular adhesion molecule-1.[26,27] Inflammatory mediators such as IL-1 and TNF-a can stimulate endocan expression, leading to increased circulating levels of endocan, which may indicate the presence and severity of inflammation. Conversely, a decrease in endocan levels can occur after inflammation subsides. However, studies investigating serum endocan levels in obesity have reported conflicting results. Some studies have found lower endocan levels in obesity and a negative correlation between endocan and BMI.[15,16,28] On the other hand, some studies have reported a positive correlation between BMI and serum endocan levels.[29,30] These discrepancies may be attributed to differences in the characteristics of the study populations, as conditions such as polycystic ovary disease, overt hypothyroidism, and severe cardiometabolic states could have unidentified implications on the conflicting results.[29,30]

In our study, we observed a strong association between pre- and post-BS endocan levels and BMI, with a more pronounced correlation between post-BS endocan levels and BMI (r2=0.497 vs r2=0.221). We speculate that this may be attributed to the alleviation of other confounding factors that interfere with the association between obesity and endocan. The weight loss following BS also provided substantial metabolic improvement in lipid profile, HOMA-IR, fasting insulin, HbA1c, and ALT (probably related to steatohepatitis). HOMA-IR and HbA1c did not correlate to BMI surprisingly, however, diabetic patients with relatively low BMI (mostly in Class 2) were the main causes of this result, since their HgbA1c and HOMA-IR levels are expected to be higher.

Recent studies have underscored the potential impact of BS in reducing obesity-related chronic low-grade inflammation, with lasting effects observed up to four years post-surgery.[31,32] Notably, both Roux-en-Y Gastric bypass and sleeve gastrectomy have demonstrated comparable efficacy in mitigating inflammation, as evidenced by a reduction in markers such as CRP, high-sensitivity CRP, and leukocyte count.[32,33]

In our study, we investigated the impact of sleeve gastrectomy on reducing serum endocan, IL-6, and CRP levels. We studied endocan as an inflammatory marker for the first time in the context of bariatric surgery and found a compatible correlation between serum endocan level and the previously examined markers, IL-6 and CRP levels.

Although the previous studies presented substantial short and long-term survival benefits of BS, the short and long-term mortality predictors in obese individuals remain lacking and objective of debate.[34,35] Whether some inflammation markers may be predictors of mortality in this regard needs clarification in the future. In this study, we have presented evidence of an association between serum endocan, IL-6, and CRP and obesity and BS. These findings may provide future research endeavors aimed at elucidating the potential roles of these markers in predicting mortality among obese individuals.

Limitations of the Study

The study included a relatively small number of participants (32 patients), which may limit the generalizability of the findings. A larger sample size would provide more robust and representative results. The study did not include a control group of individuals with obesity who did not undergo sleeve gastrectomy. Without a control group, it is difficult to attribute the observed changes in inflammatory markers solely to the surgical intervention. The follow-up period in this study was limited to 3 months after sleeve gastrectomy. Longer-term follow-up would be valuable to assess the sustainability of the observed reductions in inflammatory markers and to evaluate the long-term effects of the surgery on weight loss and metabolic outcomes. The study did not perform predictive and sensitivity tests using receiver operating characteristic (ROC) analysis for the inflammatory markers. This analysis could have provided insights into the diagnostic accuracy and predictive value of these markers in relation to sleeve gastrectomy. The study population consisted of patients who underwent sleeve gastrectomy, which may introduce selection bias. The findings may not be applicable to all individuals with obesity, particularly those who are not eligible for or choose not to undergo bariatric surgery. The study did not thoroughly assess or control for potential confounding factors such as diet, exercise, or medication use, which could influence the observed changes in inflammatory

markers and metabolic outcome. The study was conducted at a single center, which may limit the generalizability of the findings to other clinical settings or populations.

Conclusion

This study demonstrates that sleeve gastrectomy (BS) is effective in reducing inflammatory markers such as endocan, IL-6, and CRP in individuals with obesity. The findings support the role of BS in addressing the chronic inflammatory state associated with obesity. Moreover, those parameters are probably useful in evaluating the inflammatory status of obesity and effectiveness of weight reduction treatments such as BS. Further research is needed to explore the potential benefits of more aggressive weight loss strategies in reducing inflammation and improving metabolic health in individuals with obesity.

Referee Evaluation Process

Externally peer-reviewed.

Ethics Committee Approval

A local ethics committee approval was obtained from the Medicana International Ankara Hospital Ethics Committee with the number BSH 2022/19. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Informed Consent

All patients signed the free and informed consent form.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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