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Effect of Surgically-Induced Weight Loss on Leukocyte Indicators of Chronic Inflammation in Morbid Obesity

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Background: Recent evidence suggests that morbid obesity is a chronic inflammatory condition that may be associated with immune dysfunction. To test this hypothesis, we investigated several leukocyte cell surface markers of chronic inflammation and followed their response to surgically-induced weight loss.

Methods: 26 patients having Roux-en-Y gastric bypass (RYGBP) for morbid obesity (BMI>40) were compared to 10 normal controls (BMI<25). Relative monocyte and neutrophil frequencies and expression of the activation antigens CD11b (adhesion molecule), CD16 (Fc receptor), and CD62L (L-selectin), were evaluated by flow cytometry preoperatively and at 1, 3, 6 and 12 months after RYGBP. Cases served as their own controls but were also compared to non-obese controls. The results were statistically analyzed using Student's t-test and ANOVA for parametric values and Mann-Whitney along with Kruskal-Wallis ANOVA for nonparametric values

Results: The control group had mean age 37 ± 7.6 with mean 23 ± 2.5 and no comorbidities. The mean age of the sample group was 40.36 ± 13.7 with mean BMI 52 ± 8.2 . The neutrophil and monocyte relative frequencies of CD11b (monocytes and neutrophils), and CD16 (neutrophils only) were comparable to controls at baseline and did not change significantly with weight loss throughout the study period. However, a significant reduction of CD62L (L-selectin) expression was noted in monocytes and neutrophils at baseline (neutrophils 103 vs 240 gmf, $p<0.001$) (monocytes 104 vs 246 gmf, $P<0.001$) when compared to normal controls. Levels of L-selectin normalized by 6 months in both monocytes and neu-

trophils, and by 12 months had become abnormally elevated in monocytes (monocytes 391 gmf, $P=0.007$); in neutrophils, there was an upward trend that did not reach significance. The expression of the LPS receptor CD14 in the study group was elevated significantly compared to controls at baseline (1129 vs 719 gmf, $P=0.004$); this marker appeared to return to normal by 3 months. Monocyte CD14+/CD16+ subset percentage were also elevated significantly at baseline (14.3% vs 5.25%, $P<0.001$), declined throughout the time period but was still significant at 1 year (8.8%, $P<0.001$). Eosinophil percentages were elevated at baseline (3.3% obese vs 1.8% controls, $P=0.003$) and remained so throughout the time period.

Conclusion: Deficiencies in the immune system of morbidly obese individuals include elevated levels of eosinophils, monocyte CD14, and monocyte CD14+/CD16+ subsets, with depression of monocyte and neutrophil CD62L. These abnormal levels reverse rapidly with surgically-induced weight loss. RYGBP is not only a weight loss operation but also appears to be an immune restorative procedure.

Key words: Flow cytometry, L-selectin, CD11b antigen, CD14 antigen, morbid obesity, bariatric surgery, gastric bypass, monocyte, CD62L antigen, CD16 antigen, eosinophil, inflammation, neutrophil

Introduction

In 1934 Seifert, using epidemiological methods, confirmed the observations of countless physicians that obesity is associated with increased morbidity and mortality.¹ Progress, however, has been slow in delineating the defects that place the morbidly obese at higher risk for immunologic complica-

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tions such as cancer and infections. Indeed, the higher morbidity and mortality may be the result of cellular dysfunction in the presence of a chronic inflammatory state which possibly exists in morbid obesity.² To test this hypothesis, we chose several unique markers of inflammation in a morbidly obese population and compared them to normals. We subsequently used these and other receptors to determine the effects of the long-limb Roux-en-Y gastric bypass (RYGBP), as described by Brolin, on those cellular markers.³

Methods

The Institutional Review Board of Nassau University Medical Center reviewed and approved the protocol. All patients gave informed consent before participation in the study.

Ten non-obese subjects with no comorbidities and BMI ≤ 25 were recruited from the staff at University Hospital to function as normal controls. They were compared with 27 consecutive patients undergoing RYGBP for morbid obesity who had a BMI ≥ 40 . Exclusion criteria included steroid use, history of cancer or asthma and those with documented immunologic deficiencies. All morbidly obese patients had a standardized history, physical and laboratory evaluation performed as part of their preoperative work-up, as noted in the International Bariatric Surgery Registry. Each patient had medical clearance before the operation.

Peripheral blood samples were obtained in sodium heparin tubes from all patients preoperatively and at 1, 3, 6 and 12 months postoperatively. Samples were drawn from patients between 10 am and 2 pm, except the first five patients preoperatively who were drawn between 7 am and 8 am. Blood samples were processed for flow cytometric analysis within 4 hours of drawing.

A mixed leukocyte population was prepared from each blood sample by hypotonic lysis of the erythrocytes and by subsequent centrifugation and washing with phosphate-buffered saline. The cells were then incubated on ice with antigen-specific monoclonal antibodies (CD14, CD16, CD11b, CD62L) conjugated with either fluorescein isothiocyanate (FITC), phycoerythrin (PE), or allophycocyanin (APC) obtained from Becton-Dickinson Biosciences (San Jose, CA). The cells were subsequently washed, and then fixed with 1% paraformaldehyde and stored at 4°C in the dark. The antigen panels were analyzed on a FACS Vantage flow cytometer (BDIS, San Jose, CA) after optimization with appropriate controls. A minimum of 20,000 cells per tube were acquired for subsequent data analysis.

The flow cytometry data was evaluated using FlowJo analytical software (Tree Star Inc., Palo Alto, CA). Specific leukocyte sub-populations were gated using side scatter and CD14 plots. From these gates, relative percentages of monocytes, lymphocytes, and polymorphonuclear leukocytes (PMNL) were obtained. Further gating of the PMNL subset by side scatter vs CD16 was used to separate neutrophil and eosinophil subsets. Leukocyte antigen expression, measured as geometric mean fluorescence (gmf) of the bariatric group was compared to themselves preoperatively and up to 12 months after the RYGBP. They were also compared to the normal control group using parametric statistical tests (Student's t-test and ANOVA) with Sigma Stat software (SPSS Inc., Chicago, IL). Statistical significance was set at $P \leq 0.05$, and all values are expressed as mean \pm standard deviation. Graphical representations in the figures are Tukey box plots with a mean line outlined by the 25th and 75th percentiles, and the 10th and 90th percentiles as error bars. Outliers are represented by dots.

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Results

Our sample group was made up of 26 consecutive patients. There were 25 females and one male with a mean BMI of 52 ± 8.2 (range 41 to 72) and a mean age of 40 ± 13.8 (range 18 to 60). These patients had a large spectrum of co-morbidities that afflict the morbidly obese, and those conditions are depicted in Table 1. The lists of medications being taken by our morbidly obese patients are depicted in Table 2. Of the patients, 46% (12/26) were on no medications at all. The ethnic origins of the patients are shown in Table 3.

The control group consisted of 12 females and

Table 1. Comorbidities

Hypertension	14
Exertional dyspnea	13
Arthritis	10
Smoker	8
Venous stasis	7
Hypothyroidism	3
Type-II diabetes	3
Rheumatoid Arthritis	1

three males. Their ethnic origins are also shown in Table 3. Their mean age was 37 ± 7.6 (range 30 to 57) with a mean BMI of 23 ± 2.5 (range 21-26), and no comorbidities.

All but one patient in the study group responded well to surgery, with mean BMI going from 52 preoperatively to 47, 42, 38 and 35 at 1, 3, 6, and 12 months respectively ($P < 0.001$).

There was no apparent difference in the relative monocyte and neutrophil percentages at baseline (neutrophil control 43.4% vs 46.7% obese $P = 0.464$, monocyte control 5.7% vs 5.4% obese $P = 0.675$), and this relationship did not change with weight loss (neutrophil 48.6%, 50.77%, 49.5%, 51%, at 1, 3, 6, and 12 months, respectively) (monocyte 5.5%, 5.0%, 5.3%, 6.0% at 1, 3, 6, and 12 months respectively).

The neutrophil subset can be further delineated by examining the side scatter vs CD16 distribution. This plot yields two distinct groups of PMNLs – neutrophils and eosinophils. Eosinophils express CD16, but exhibit a distinctly weaker signal than neutrophils. While there was no apparent difference in the neutrophil percentages, the eosinophil subset was significantly greater in the obese group

Table 2. Preoperative medications

Fluoxetine	3	Prazosin	1
Isophane Insulin Suspension	3	Synthroid	3
Nifedipine	3	Glipizide	3
Diltiazem Hydrochloride	2	Diazepam	2
Quinapril Hydrochloride	2	Metformin	2
Clonidine Hydrochloride	2	Naproxen Sodium	1
Lovastatin	1	Polocarpine	1
Zolpidem	1	Clonazepam	1
Azathioprine	1	FeSO4	1
Famotidine	1	Losartan/HCTZ	1
Hydroxychloroquine Sulfate	1	Furosemide	1
		Benazepril	1
		Orlistat	1

Table 3. Ethnic origins

Control Group (N=15)	
Females	
Caucasian	4
Hispanic	3
African American	3
Indian female	1
Males	
Caucasian	3
Indian	1
Bariatric Group (N=26)	
Females	
African American	13
Caucasians	6
Hispanics	6
Males	
Caucasian	1

compared with controls (3.35% vs 1.96%, $P = 0.003$). This relationship continued throughout the time period (2.9%, 2.9%, 3.7%, 3.0% at 1, 3, 6, and 12 months respectively) (Figure 1).

A subset of monocytes exists that more strongly co-expresses both CD14 and CD16 (CD14+/CD16+). This subset normally constitutes 5% to 8% of circulating monocytes and is responsible for cytokine production in acute and chronic inflammation.¹⁷⁻²² The percent of monocytes in the CD14+/CD16+ subset was markedly higher in the morbidly obese group preoperatively when com-

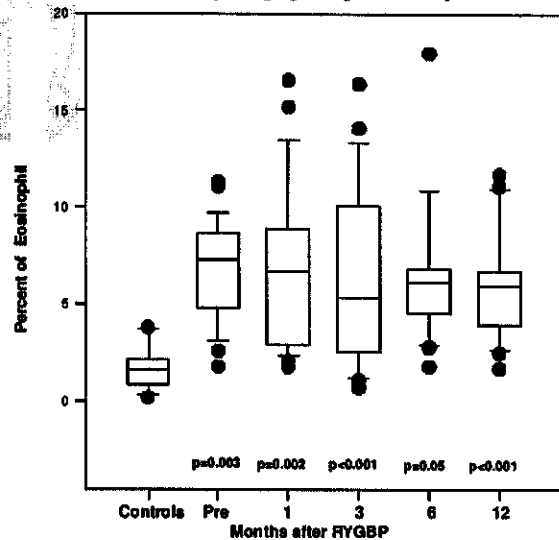


Figure 1. Eosinophil percentages are elevated when compared to controls preoperatively and continue to be elevated to 12 months.

pared with the normal controls (14.3% vs 5.25%, $P<0.001$). This difference persisted at 1, 3, 6, and 12 months respectively (16.1%, $P<0.001$; 13.4%, $P=0.036$; 11.3%, $P<0.001$, 8.8%, $P<0.001$). When the patients are analyzed for phenotype expression over time there is a significant decline from preoperative levels to 12 months ($P<0.001$)(Figure 2).

The expression of the FcRIII receptor CD16, the low-affinity receptor for IgG, was not significantly different on the obese patients' neutrophils in comparison with those of the control group (gmf 298 vs 267 gmf, $P=0.888$). This relationship did not change with weight loss (285 $P=0.560$, 302 $P=0.395$, 226 $P=0.267$, 306 $P=0.237$) at 1, 3, 6 and 12 months respectively. When obese patients preoperative values were compared through time, there was no change with weight loss ($P=0.100$).

We also chose to look at two adhesion antigens CD11b and CD62L (L-selectin) expression on leukocytes. CD11b showed no difference on monocytes or neutrophils from the controls at baseline (monocyte non-obese controls 577 gmf vs 515 gmf in morbidly obese $P=0.945$) (neutrophils non-obese controls 498 gmf vs 424 gmf in morbidly obese cases, $P=0.436$). Surprisingly, there was also no significant difference following RYGBP, with the neutrophil expression of CD11b being 428, 380, 420 and 499 gmf at 1, 3, 6 and 12 months respectively. The monocytes also did not show any significant differences when compared with con-

trols, with gmf being 550, 478, 550, 573 at 1, 3, 6, and 12 months respectively.

CD62L, a selectin that mediates the initial tethering and rolling to the endothelial surfaces, was decreased significantly with respect to controls in both monocytes and neutrophils (monocytes 103 vs 269 gmf, $P<0.001$) (neutrophils 303 vs 102 gmf, $P<0.001$). This relationship was still significant at 1 month (monocytes 159 gmf, $P<0.001$) (neutrophils 152 gmf, $P<0.001$). However, by 3 months postoperatively, the trend normalized and continued to 6 months (monocytes 207 gmf, $P=0.143$ and 253 gmf, $P=0.724$ at 3 and 6 months respectively) (neutrophils 229 gmf, $P=0.086$ and 244 gmf, $p=0.200$, at 3 and 6 months respectively) (Figure 3). By 12 months, however, L-selectin was abnormally elevated in monocytes when compared with controls (monocytes 384 gmf, $P=0.004$). In neutrophils, the trend continued upward and approached statistical significance when compared with controls (neutrophils 400 gmf, $P=0.061$) (Figure 4). When obese patients are compared to themselves, there was a statistically significant change from baseline to 12 months in both monocytes and neutrophils ($P<0.001$ in both).

The last receptor studied was CD14 or the lipopolysaccharide receptor (LPS). Peripheral blood monocytes strongly express CD14. This molecule interacts with other receptors to mediate a variety of inflammatory functions. In the mor-

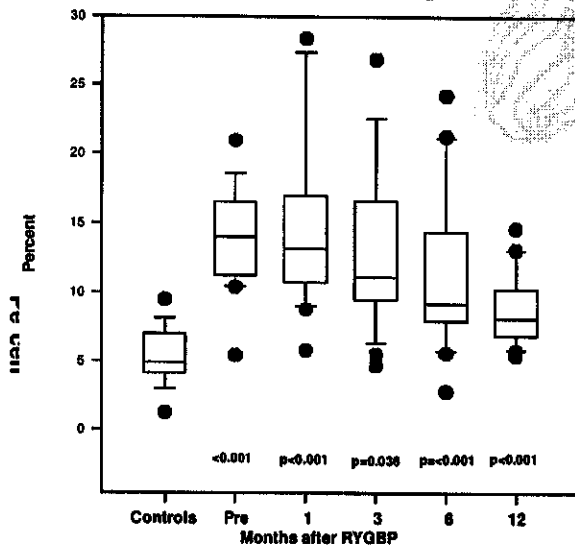


Figure 2. Monocyte CD14+/CD16+ percentages are elevated when compared to controls preoperatively and decline throughout the study period.

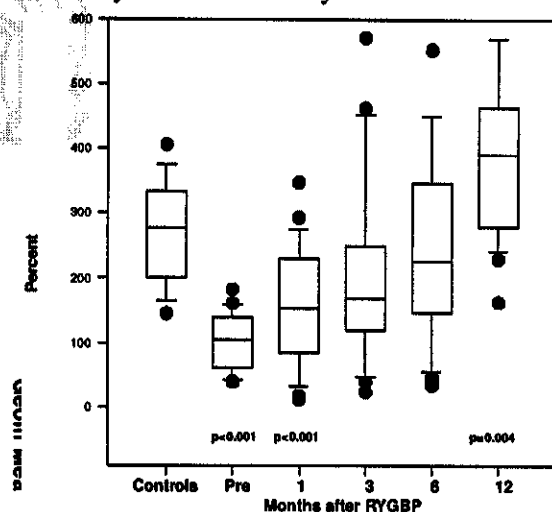


Figure 3. Monocyte CD62L (L-selectin) expression is decreased when compared to controls preoperatively and normalizes by 6 months. By 12 months, it is abnormally elevated.

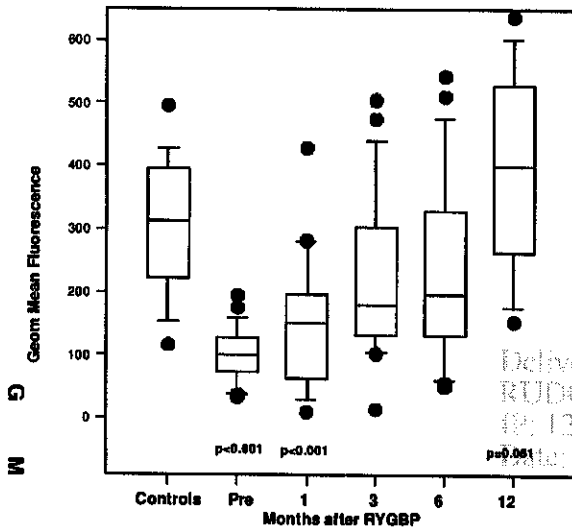


Figure 4. Neutrophil CD62L (L-selectin) expression is decreased when compared to controls preoperatively and normalizes by six months. By 12 months it is elevated.

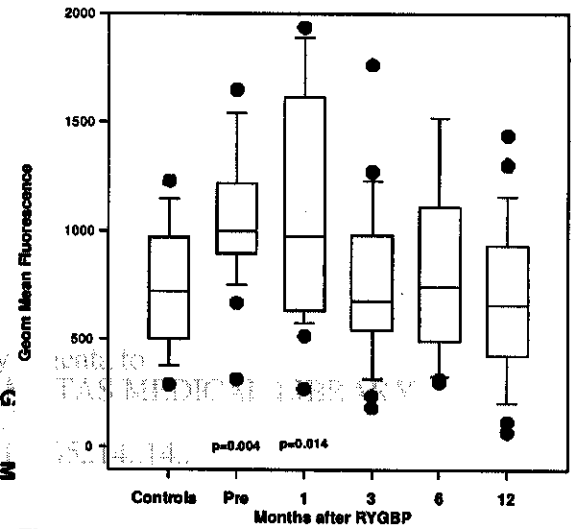


Figure 5. Monocyte CD14 (LPS receptor) expression is elevated when compared to controls preoperatively and normalizes by 3 months.

bidly obese group, we observed a significantly higher expression of CD14 than that of the normal control group at baseline (1129 vs 719 gmf, $P=0.004$). This trend continued to 1 month postoperatively (1150 gmf, $P=0.014$). By 3 months, however, the difference had narrowed (775 gmf, $P=0.718$), and this normalization continued to 6 and 12 months with the gmf being 894 ($P=0.338$) and 681 ($P=0.647$) at 6 and 12 months respectively (Figure 5). When obese preoperative levels are compared with 12-month levels, a significant difference is also noted ($P=0.004$)

There was one patient who did not lose weight after RYGBP. Her receptor levels did not significantly change throughout the study when compared with preoperative levels and non-obese controls.

In looking at diabetes, medications, sample acquisition time, and smoking as confounding variables, the values were not significantly different from other non-diabetic, non-medicated, mid-day sample acquisition, or non-smoking morbidly obese patients at baseline when compared using student's t-test in all cell surface receptors (CD11b, CD14, CD16, CD62L) and in relative leukocyte percentages (monocyte, neutrophil, CD14+/CD16+ subset). Following RYGBP, these subsets experienced the same trends throughout the study period as our general population (rising L-selectin

in neutrophils and monocytes, falling CD14+/CD16+ percentages in monocytes, falling CD14 levels in monocytes, consistent CD11b levels). In addition, there was no independent variable that appeared to correlate with weight loss or BMI using Pearson's product coefficient or linear regression.

Discussion

Morbid obesity predisposes individuals to higher rates of breast, colon, and prostate cancer and wound infections.⁴⁻⁵ Recognizing this fact, researchers have made numerous attempts to characterize the function of monocytes and PMN *in vitro*. Monocytes in the obese have elevated levels of oxidative burst^{6,7} and reduced ability for monocyte maturation,⁸ and retain their ability to phagocytize normally⁶⁻⁷ when compared with non obese normals *in vitro*.

Neutrophils from obese individuals have demonstrated a decrease not only in glucose oxidation⁹ and bactericidal capacity,^{10,11} but also in intercellular killing¹² when compared with normals. However, they have increased ability for phagocytosis and oxidative burst, and both these variables correlated with BMI.⁶ Additionally serum from mildly to moderately obese individuals (BMI >25)

has been shown to cause a decrease in the ability of neutrophils from normal controls to undergo chemotaxis and intracellular microbial killing while the ability for phagocytosis is retained.¹³

Currently, controversy exists in regard to absolute counts of monocytes with obesity.^{6,7,14} This fact is important, because elevated absolute counts of monocytes have been shown to be independent risk factors for cancer and coronary heart disease.¹⁵⁻¹⁸ We were able to determine relative neutrophil and monocyte frequencies using flow cytometric techniques. We found that the relative neutrophil frequencies did not appear to be different from our controls throughout the time period studied, and these findings did not change with weight loss. These findings contradict those of Nieman who found that there is elevated monocyte counts in obesity.^{6,7} It is important to note that our sample series was larger than Nieman's and our technique was different. These findings did not change with weight loss.

However, in subset analysis of monocytes and neutrophils, we found two variables that were significantly elevated. The first is the monocyte CD14+/CD16+ subset. This cell population represents a proinflammatory subtype that exhibits features of tissue macrophages.¹⁹ These cells also produce a disproportionately large share of inflammatory cytokines TNF α , IL-1 β , IL-10. In chronic inflammatory states such as acute vasculitis, active HIV, Kawasaki disease, and chronic hemodialysis, this cytokine-producing subset is greatly expanded, similar to levels seen in morbid obesity.¹⁹⁻²⁴ Importantly, levels of this inflammatory cell appear to normalize within 3 months after RYGBP.

The second subset expansion was noted in the eosinophil subset of neutrophils. This subset was elevated at baseline and continued throughout the time period. We believe that this may reflect the chronic inflammation that results from obesity, because our average BMI is 35 at 12 months (down from 51 preoperatively).

In addition to relative cell percentages, we investigated leukocyte adhesion molecules, because of the unique combination of normal phagocyte ability in obesity and higher incidence of wound infections. The two molecules CD11b and CD 62L are adhesion molecules that work together to allow the leukocyte to migrate to sites of inflammation.²⁵ The

process is initiated by CD62L, arresting the laminar flow of the leukocyte and initiating rolling. Once rolling is begun then CD11b will cause adhesion to the endothelial wall and diapedesis can begin. Without CD 62L, CD11b is unable to begin diapedesis on its own. CD62L and CD11b generally rise together in acute inflammatory conditions such as trauma.²⁶ In chronic conditions, however, such as vasculitis or HIV, CD11b remains constant while CD62L is shed from the surface of monocytes and neutrophils.²⁷⁻²⁹ Our findings of decreased CD62L in both neutrophils and monocytes at baseline suggest an inability for the cells to migrate to sites of inflammation. Taken in conjunction with normal CD11b levels, it becomes apparent that morbid obesity results in a chronic inflammatory state. The depressed levels of CD62L were reversed with weight loss by 3 months. Unexpectedly these levels then continued to rise postoperatively to levels above those of non-operative controls. This may represent continued stimulation present in the system of obese patients, as our patients' average BMI at 12 months was 35, or possibly an overshoot phenomenon. This concept of inflammation associated with BMI is correlated with the findings of elevated C-reactive protein in patients with BMI >25.³⁰

Fc receptors (FcR) are expressed on all cells of the immunologic system as well as epithelial and endothelial cells. These molecules link the humoral and cellular immunity by binding the antibody to effector cells.³¹ FcR receptors play a variety of regulatory roles in the human body, which include: regulation of inflammatory mediator production; regulation of oxygen radicals production; and regulation of antibody production in antibody dependent cellular cytotoxicity (ADCC).³² Our study found that the expression of this antigen was not different when compared with normals, and did not change throughout the study period. This finding does not help to explain the decreased bactericidal capacity seen in morbid obesity.^{10-13,33-35}

CD 14, also known as the LPS receptor, is responsible for the binding of lipopolysaccharide (LPS) and peptidoglycan. The interaction of this receptor with those antigens induces the production of TNF, IL-6, IL-10, IL-1 β and IL-1ra seen in gram-negative sepsis, gram-positive sepsis, and chronic inflammation.³⁶⁻³⁸ This receptor was ele-

vated at baseline and this continued to 1 month, but by 3 months the values had normalized, and this trend continued to 1 year.

The above trends seem to highlight the hypothesis that obesity is a chronic inflammatory condition. This possibility was first suggested by several authors in 1999, when C-reactive protein was shown to correlate independently with BMI.^{31,39-41} They additionally showed that CRP level elevation was independently correlated with several measures of obesity and not subject to confounding variables.³⁹ These findings have been confirmed by other authors.^{41,42} Especially significant in our study is the fact that the cellular abnormalities associated with chronic inflammation appear to be reversible following RYGBP. Our findings, however, do not explain the rapid reversal of inflammatory indicators despite the persistence of mild obesity.

Our study has approached obesity and its treatment in a novel way and as with any approach it will be subject to criticisms. Foremost among these would be the effect of diet, exercise, and medication use on the studied parameters. We counseled all patients to participate in an exercise program after surgery and eat a low fat diet; however, compliance was not monitored. We could not avoid all medications, because morbidly obese patients often take medications because of associated comorbidities. We did try to compensate for this fact by comparing our patients on medications to our patients on no medications and with no comorbidities. In our study, we found no statistical evidence to suggest that medication plays a role in cell surface receptor expression in morbid obesity.

Conclusion

Obesity needs to be viewed not only as a condition of excess adiposity but also as a state of chronic inflammation. This condition was manifested in our study by elevation of CD14+/CD16+ monocyte subset, elevation of eosinophils, elevation of monocyte CD14 (LPS receptor), normal levels of monocyte and neutrophil CD11b with depressed levels of monocyte and neutrophil CD 62L (L-selectin), and depressed levels of CD16. This

Enhanced Immune Function Following Gastric Bypass

chronic inflammation causes immune suppression, manifested by shedding of L-selectin that could possibly result in the inability to migrate to sites of infection by monocytes and neutrophils. Perhaps more significant than the immune suppression and chronic inflammation seen with obesity is the fact that almost all the parameters of immune function and chronic inflammation studied appear to be reversible within 6 months after bariatric surgery. This effect is independent of diabetes, smoking, or medication. Indeed, our study supports the fact that RYGBP renders our patients immunocompetent even before they have lost 25% of their excess adiposity. Further study of the role of lymphocytes, cytokines and other immune markers is warranted, as they could possibly play a role in the alteration of leukocyte cell surface receptor expression. Obesity is a complex condition with many intricacies worth identifying, because this debilitating disease affects over 50 million people.

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