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Dysfunctional Immune-Privilege In Morbid Obesity: Implications and Effect of Gastric Bypass Surgery

D. R. Cottam, MD; P. A. Schaefer, PhD; G. W. Shaftan, MD; L. D. G. Angus, MD

Nassau University Medical Center, Department of Surgery, East Meadow, NY, USA

Background: Despite the epidemiological evidence linking obesity and cancer, there has never been a causal link. We believe the chronic inflammation present in obesity may predispose the obese to cancer through Fas-receptor over-expression and L-selectin under-expression in leukocytes, and elevated Fas ligand secretion in tumors affecting the morbidly obese.

Methods: Leukocytes from 25 patients having gastric bypass surgery were compared to 15 normal controls preoperatively and at 1, 3, 6, and 12 months postoperatively using flow cytometry to measure CD3, CD4, CD8, CD56, CD62 (L-selectin), CD 69, and CD95 (Fas antigen) expression on T lymphocytes, B lymphocytes, natural killer cells, and neutrophils.

Results: The percentage of CD95+T cells was significantly elevated from controls (69.4% vs 56%, $P=0.005$). This difference persisted through 1 month postoperatively. Furthermore, expression of CD95 per cell, was significantly greater in these patients than that of the controls (80.2 vs 62.6 gmf, $P=0.018$) preoperatively, and this continued to 1 month. Polymorphonuclear cells also displayed a similar elevation in CD95 gmf expression preoperatively (54.1 vs 40.7 gmf, $P=0.023$) which normalized by 3 months. Natural killer cells did not display elevated numbers of CD95 gmf preoperatively, but they did experience a significant decline by 12 months. Additionally, there was significant reduction in the number of naive T cells [(T cells without L-selectin (CD62L)], when compared to normals preoperatively (41.8% vs 51.3%, $P=0.001$). There was no statistical difference between the postoperative patients and the controls by 3 months. CD69 was not different at baseline from controls in T or B cells, but there was a significant decrease by 12 months.

Conclusion: The reduced expression of L-selectin combined with the elevated levels of CD95 suggests that morbid obesity predisposes patients to sites of

immune privilege. This could be the mechanism for increased rates of cancer and wound infections seen in obesity. Surgically-induced weight loss eliminates these risk factors.

Key words: Morbid obesity, cancer, apoptosis, chronic inflammation, L-selectin, Fas antigen, CD62L, CD95, lymphocyte, neutrophil, flow cytometry, immune privilege, bariatric surgery, gastric bypass

Introduction

In the past, morbid obesity has been viewed as a condition of excess adiposity. It should also be viewed, however, as a condition of chronic inflammation that results in immune dysfunction. Our previous studies on monocytes and neutrophil dysfunction in morbid obesity demonstrated marked phenotypical abnormalities as a result of chronic inflammation in monocytes and neutrophils.^{1,2} These abnormalities likely have a major impact on the way the morbidly obese patients respond to stresses such as operation, trauma, and infection. These abnormalities are quickly reversed with gastric bypass surgery.

Previous attempts to characterize lymphocyte function in obesity have included measurement of total lymphocyte counts,^{3,4} total natural killer cell counts,⁵ natural killer cell activity,^{5,6} total T and B cell counts,⁵ mitogen induced lymphocyte proliferation,^{3,6-11} and measurement of serum immunoglobins.¹¹ However, very few of these studies have been done in morbidly obese patients and even fewer monitored their response to weight loss.^{4,7,10}

In order to further characterize the role of obesity on the immune system, we expanded the scope of

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Reprint requests to: Daniel R Cottam, 31 Woodpecker Lane, Levittown, NY 11756, USA. E-mail: danamycottam@yahoo.com

our research to include lymphocytes and have looked at several cluster determinates (CD) on lymphocytes and neutrophils. The first of these CD3 is a universal T antigen used to identify T cells from other lymphatic cells. CD4 is a class II MHC binding antigen and is a cell surface marker for helper T cells. CD8 binds to class I MHC and is a cell surface marker for cytotoxic or suppressor T cells. CD19 is a B cell marker. CD56 is a natural killer (NK) cell marker. CD62L is a member of the selectin family of glycoproteins that is expressed on all immunologic cells including lymphocytes. These receptors cause a low-affinity interaction, resulting in "rolling" of the lymphocyte or neutrophil along the endothelial surface. Without this interaction, lymphocytes are unable to leave the vascular space. CD95 is the last molecule studied and it directs apoptosis (cell death) in almost all cells of the body and is an important receptor in the pathogenesis of infections and cancer.

Methods

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

Fifteen non-obese subjects with no comorbidities and body mass index (BMI) ≤ 25 were recruited from the staff at University Hospital to function as normal controls. They were compared to 27 consecutive patients undergoing operation for morbid obesity who had BMI ≥ 40 . Exclusion criteria included steroid use, history of cancer, 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 (IBSR). Each patient had medical clearance before gastric bypass.

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, with the exception of 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 (CD3, CD4, CD19, CD56, CD69, CD62L, CD95,) 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 was 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. Lymphocyte antigen expressions, measured as geometric mean fluorescence (gmf), of the bariatric group were compared to themselves preoperatively and up to 12 months postoperatively. 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 were 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.

Results

There were 26 females and one male in our obese sample group that had a mean age of 40 ± 13.8 yrs (range 18 to 60) and typical spectrum of comorbid conditions that afflict the morbidly obese (Table 1).

Table 1. Comorbidities of bariatric surgical patients preoperatively

Hypertension	14
Exertional dyspnea	13
Arthritis	10
Smokers	8
Venous stasis	7
Hypothyroidism	3
Non-insulin dependent diabetes	3
Rheumatoid Arthritis	1

The average BMI of our sample group was 52 ± 8.2 kg/m² (range 41 to 72) (Table 2).

The control group was comprised of seven females and three males. Their mean age was 37 ± 7.6 yrs (range 30 to 57), and they had no comorbidities. Their mean BMI was 23 ± 2.5 kg/m² (range 21-26).

When the absolute percentage of lymphocytes was compared to total leukocytes, B cell percentages of total lymphocytes, NK cell percentages of total lymphocytes, T cell percentages of total lymphocytes, and T cell subsets (CD4+/CD8+, CD4+/CD8-, CD4-/CD8-, CD4+/CD8+, CD4/CD8 ratio) between the obese and non-obese, no difference was found preoperatively (Table 2). Likewise, B cell percentages of lymphocytes, NK cell percentages of lymphocytes, T cell percentages of lymphocytes,

Table 2. Percentages of lymphocytes following gastric bypass

	Obese Mean	Controls Mean	P-value*
BMI	52.0 ± 8.2	23.0 ± 2.5	<0.001
AGE	40.0 ± 13.8	37.0 ± 7.6	0.312
Total Lymph %	26.7 ± 10.8	28.7 ± 10.8	0.523
B cell			
% of lymph	$28.7 \pm 8.9\%$	$29.7 \pm 11.2\%$	0.766
T cell			
% of lymph	$65.9 \pm 12.4\%$	$71.2 \pm 17.1\%$	0.103
CD4+/CD8+%	$2.6 \pm 2.5 \%$	$1.8 \pm 1.4 \%$	0.216
CD4+/CD8-%	$61.6 \pm 9.6 \%$	$62.1 \pm 8.1\%$	0.895
CD4-/CD8-%	$5.3 \pm 3.2 \%$	$5.2 \pm 3.7 \%$	0.951
CD4-/CD8+%	$30.6 \pm 9.2\%$	$30.9 \pm 7.4 \%$	0.901
CD4/CD8 ratio	$2.3 \pm 1.1 \%$	$2.3 \pm 1.2 \%$	0.962
NK cell %	$12.5 \pm 6.2 \%$	$11.3 \pm 4.1\%$	0.538

*No significant differences between obese patients and control patients

and T cell subsets (CD4+/CD8+, CD4+/CD8-, CD4-/CD8-, CD4+/CD8+, CD4/CD8 ratio) did not change throughout the study period (Table 3).

However, when naive T cell percentages were measured [defined by the presence of the adhesion molecule L-selectin (CD62L)], there was a significant depression present preoperatively (41.8% vs 51.3%, $P=0.001$). This difference persisted to 1 month postoperatively (45.2%, $P=0.02$). There was a trend toward increasing expression to 12 months that was significant from preoperative levels (41.8%, 45.2%, 50.0%, 47.4%, 52.5%, $P=<0.001$) (Figure 1).

Similar to the depressed percentages of cells expressing L-selectin preoperatively was the decrease in the numbers of molecules per T cell preoperatively (312 vs 149.4 gmf, $P=<0.001$). This difference continued through 1 and 3 months postoperatively (1 month 177 gmf, $P=<0.001$; 3 months 229 gmf, $P=0.044$; 6 months 235 gmf, $P=0.066$, 12 months 374 gmf, $P=0.103$) (Figure 2). Additionally, there was a significant change from preoperative values to 12 months ($P<0.001$).

We also measured expression of CD95 on all peripheral lymphocytes, polymorphonucleocytes (PMNs), and NK cells. There was an increase in the percentages of CD95+ T cells preoperatively when compared to total T cell population (69.4% vs 56%, $P=0.005$). This trend was significant to 1-month postoperatively (75.4%, $P=<0.001$). However, the downward trend continued at 3, 6 and 12 months (73.1%, 70.7%, 59.7%) (Figure 3).

Also, the amount of CD95 expression per T cell was elevated when compared to normals (62.6 vs

Table 3. Percentages of lymphocytes preoperatively and postoperatively

	Pre	1	3	6	12	P-value*
Total Lymph %	26.7	29.0	33.1	28.4	31.1	0.248
B cell % of lymph	28.7	30.4	34.3	29.2	31.4	0.376
T cell % of lymph	65.9	69.4	70.1	68.5	70.6	0.609
CD4+/CD8+%	2.6	2.6	2.1	2.1	2.1	0.852
CD4+/CD8-%	61.6	61.6	65.6	65.2	64.8	0.496
CD4-/CD8-%	5.3	5.2	5.3	5.7	5.2	0.995
CD4-/CD8+%	30.6	30.5	27.0	27.0	27.8	0.448
CD4/CD8 ratio	2.3	2.5	3.0	2.8	2.8	0.799
NK cell %	12.5	12.7	12.2	12.1	10.5	0.838

*There were no changes associated with gastric bypass

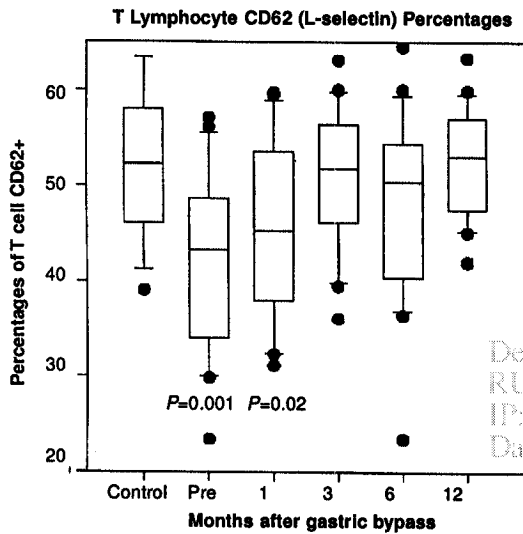


Figure 1. Graph displays the decreased numbers of cells that express L-selectin. Bariatric surgery increases the percentages of cells expressing L-selectin.

80.2 gmf, $P=0.018$). This continued to 1 month postoperatively, but continued to decline throughout the time period (1 month 92.9 gmf; $P=0.010$, 3 months 70.9 gmf, $P=0.304$; 6 months 70.7 gmf, $P=0.272$; 12 months 59.7 gmf, $P=0.691$) (Figure 4). There was a significant decline from preoperative values to 12 months ($P=0.002$)

PMNs displayed a similar increase in CD95

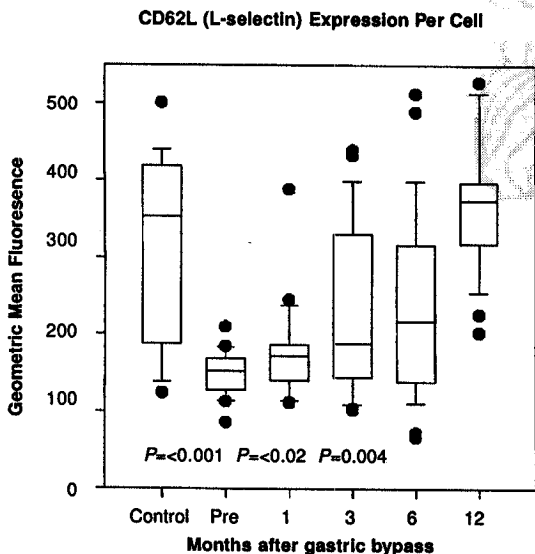


Figure 2. Graph illustrates the decreased expression of CD62L (L-selectin) in bariatric patients preoperatively. These values return to normal with gastric bypass. The decreased levels of L-selectin impair migration and recirculation in lymphocytes.

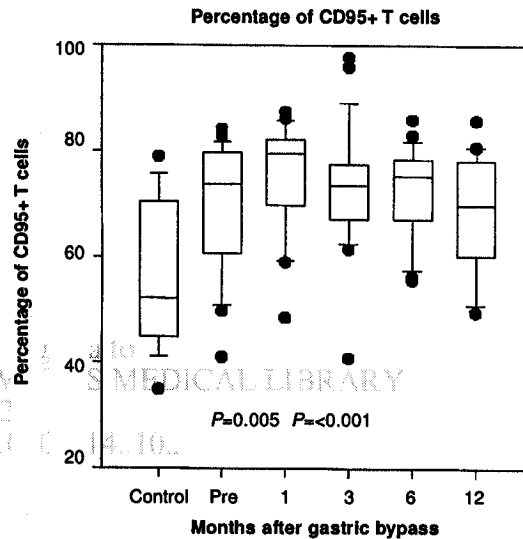


Figure 3. Graph illustrating the significant elevation of CD95 (Fas Antigen) preoperatively. We believe this plays a significant role in immune privilege seen in tumors of the morbidly obese. These values return to normal with weight loss following gastric bypass.

expression per cell preoperatively (54.1 vs 40.7 gmf, $P=0.023$). This elevation continued through 1-month postoperatively (68.0 gmf, $P=0.006$). However, by 3 months there was not a statistically significant difference (57.6 gmf, $P=0.129$) (Figure 5). This trend continued to 6 months (51.5 gmf). There also was a significant drop from preoperative levels to 12 months (54 vs 37 gmf, $P=0.005$).

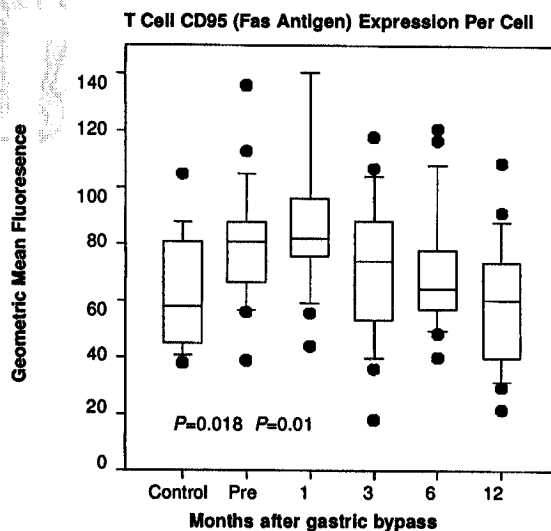


Figure 4. Graph illustrates the increased expression of CD95 (Fas Antigen) on T cells preoperatively. These values return to normal with weight loss following gastric bypass.

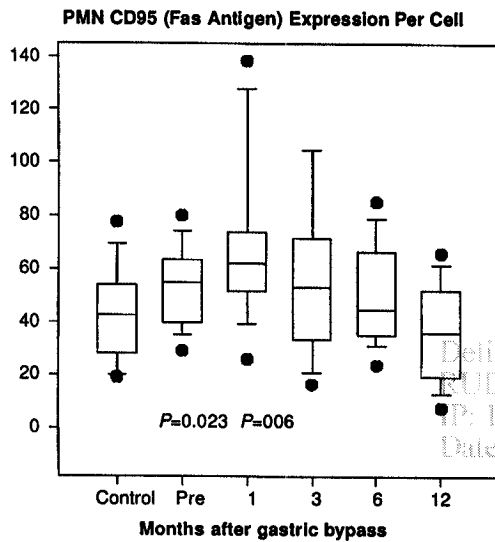


Figure 5. Graph illustrates the significant elevation of CD95 (Fas antigen) preoperatively in PMNs. We believe this plays a key role in the inability to respond to infections in the morbidly obese. These values return to normal with weight loss following gastric bypass.

Natural killer cells showed no significant increased expression of CD95 preoperatively (obese 16.7gmf vs controls 14.2 gmf, $P=0.20$), and this trend continued through 12 months (preoperative 16.7 gmf, 1 month 21.2 gmf, 3 months 16.4, 6 months 15.2 gmf, 12 months 12.6 gmf). However, there was a significant decline in obese values from preoperative levels (preoperative 16.7 to 12 months 12.6 gmf, $P=0.01$) (Figure 6).

The early activation antigen CD69 was measured on T cells, B cells, and NK cells. In T cells there was no difference preoperatively between obese and non-obese (controls 6.2 vs obese 6.4, $P=0.762$). This persisted through 12 months (preoperative 6.4 gmf, 1 month 7.1 gmf, 3 months 6.1 gmf, 6 months 5.9 gmf, 12 months 5.1 gmf). However, through time there was a significant drop from preoperative levels (preoperative 6.4 gmf vs 12 months 5.08 gmf, $P=0.002$) (Table 4, Figure 7).

B cells behaved much the same way in that there was no change preoperatively when compared to controls (controls 5.6 gmf vs obese 5.8 gmf, $P=0.501$). Yet, there was a significant difference by 12 months both in the change over time and in comparison to preoperative values [(controls 5.6 gmf vs 12 months 4.6 gmf, $P=0.016$.) (preoperative 5.8 gmf vs 12 months 4.6 gmf, $P=0.016$)] (Table 4, Figure 7).

NK Cell Expression of CD95 (Fas Antigen)

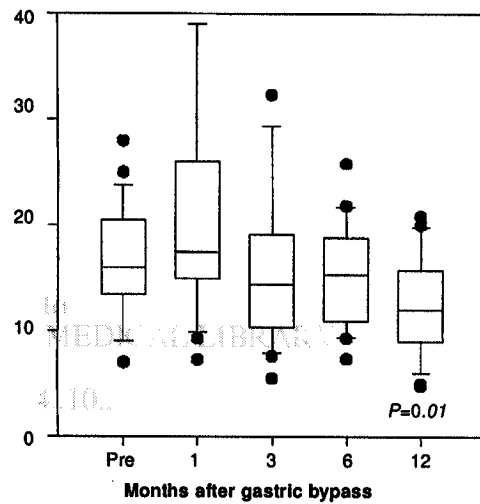


Figure 6. Graph displays the declining values of L-selectin over time on natural killer cells when compared to obese patients at baseline.

NK cells were not different at baseline from controls and this did not change when compared to controls to 12 months (controls 6.6 gmf vs 7.1 gmf obese preoperatively, $P=0.395$). Yet, there was a significant difference by 12 months when compared to preoperative values (pre 7.1 gmf vs 12 months 5.8 gmf, $P=0.025$) (Table 4, Figure 7).

Discussion

Since 1999, morbid obesity has increasingly become known as a condition of chronic inflammation. This fact was initially highlighted when several authors documented large elevations in C-reactive protein levels which correlated with BMI.¹²⁻¹⁶ Our earlier work documented how this chronic inflammatory condition affected monocytes and neutrophils in the morbidly obese.^{1,2} We further documented the decreasing inflammatory status when

Table 4. Declining values of CD69 with weight loss after gastric bypass

	Pre	1	3	6	12	ANOVA
B Cell CD69	5.6	6.4	5.9	5.3	4.6	0.002
NK Cell CD69	7.1	7.5	7.0	6.4	5.8	0.025
T cell CD69	6.4	7.1	6.1	5.9	5.1	0.002

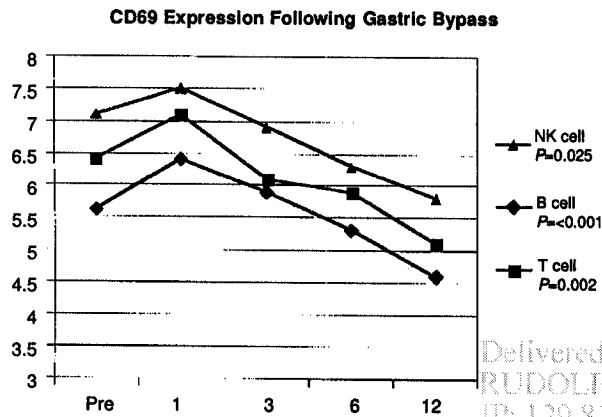


Figure 7. Graph displays the falling values of CD69 over time in the obese population in response to gastric bypass surgery.

patients underwent large-scale weight loss secondary to gastric bypass surgery.² This paper expands on the findings of the first two papers by analyzing the cell surface receptors on lymphocytes in morbidly obese patients undergoing gastric bypass and follows their response to bariatric surgical weight loss.

The first papers to focus on lymphocytes and obesity dealt with lymphocyte counts. Many authors reported no differences between obese individuals and non-obese individuals with regards to total lymphocytes, T lymphocytes, B lymphocytes, and T to B lymphocyte ratios.^{3,9,11} Contrary to this finding, Nieman reported normal NK cell counts with elevated total lymphocyte and T lymphocyte counts in adult obesity.⁵ However, with weight loss there was a decrease in NK cells,⁴ while T and B cell counts were unaffected.¹⁷⁻²⁰

In our study we agree with early authors^{3,9,11,21-22} that there is no difference between T cells, B cells, NK cells or specific CD4 CD8 ratios preoperatively or with weight loss. Nieman's studies are difficult to compare because they are much less obese in one instance, and in the other study the patient population is much too small to draw meaningful conclusions. Our study also is the first to follow lymphocytic response to long-term large-scale weight loss, and we also find that weight loss does not induce changes in percentages of lymphocytes.

L-selectin (CD62L) is an adhesion molecule that is responsible for lymphocyte tethering, rolling, and homing to tissue specific lymph nodes along high endothelial venules.^{19-20,23-27} In mice deficient of L-

selectin, there was a 99% decrease in lymphocyte migration to peripheral lymph nodes, an 88% decrease in migration to mesenteric lymph nodes, and a 50% decrease in lymphocyte migration to peyers patches.²⁸ In addition, Zouki et al²⁹ have found that C-reactive protein levels down-regulate the expression of L-selectin on the surface of neutrophils and that this affects neutrophil's ability to migrate to sites of inflammation. Matsuba et al³⁰ also have shown, in animal studies, that decreased expression of L-selectin is associated with increased susceptibility to cell death. Since we have previously shown that L-selectin expression is decreased in neutrophils and monocytes,^{1,2} and it has been firmly established that C-reactive protein levels correlate with BMI,¹²⁻¹⁶ we believe elevated levels of C-reactive protein also are decreasing L-selectin levels in lymphocytes and this will cause impairment of homing and recirculation and place those lymphocytes at higher risk of cell death. Our findings of decreased L-selectin in lymphocytes parallels our earlier findings in monocytes and neutrophils, in that the severe depression of L-selectin is reversed with gastric bypass surgery by 6 months in lymphocytes and 3 months in monocytes and neutrophils. This could help explain the more common occurrences of infections in the morbidly obese, because all leukocytes display decreased L-selectin and are therefore less able to migrate to sites of infection and inflammation and are more prone to die.

The next cell surface marker studied was CD69, also known as the activation inducer molecule, very early activation antigen, MLR-3 and Leu-23. It also is a C-type lectin-binding molecule in the same family as L-selectin (CD62L). Although the ligand for CD69 is not known, its monoclonal antibody can induce several cellular responses, including calcium influx, platelet aggregation, T cell proliferation, production and release of TNF- α , increase in NO production, increase in NK cell cytotoxicity, and neutrophil degranulation.³¹ Expression of CD69 can be induced by phorbol esters, phytohemagglutinin or CD3 monoclonal antibody in T cells, crosslinking of surface Ig in B cells, or stimulation with IL-2, interferon- α , IL-12 for activation in NK cells.³¹ Typically CD69 appears quickly after immune cell activation, usually within 30 to 60 minutes after stimulation and drops to resting levels within 72 hours.³¹ Additionally it has been linked to the induc-

tion of apoptosis when stimulated with lipopolysaccharide.³²

In our study, this molecule was not different at baseline in NK, T cells or B cells. This agrees with earlier authors in that morbid obesity is not an acute process but a chronic condition. It also mirrors our findings in monocytes and neutrophils in that CD11b is another acute activation molecule that is upregulated with acute activation. CD69 like CD11b was not upregulated.^{1,2} Throughout the study period, however, the levels gradually decline until B and NK cells were significantly different from controls at 12 months and NK, B and T cells were different from baseline obese patients using ANOVA. This leaves the impression of decreased activation through time as the weight loss progresses (Table 4, Figure 7).

The last cell surface molecule studied was CD95, the Fas antigen. This member of the TNF family directs apoptosis in almost all cells of the body.^{33,34} "Under normal circumstances the Fas receptor CD95L plays an important role mainly in three types of physiologic apoptosis: 1) peripheral deletion of activated mature T cells at the end of an immune response; 2) killing of targets such as virus-infected cells or cancer cells by cytotoxic T cells and by natural killer cells; and 3) killing of inflammatory cells at "immune-privileged" sites such as the eye.³⁴ The best example of immune privilege being induced using CD95 can be seen with the overwhelming success of corneal transplants despite being on no antirejection medications.^{35,36} Essentially the eye secretes CD95L (Fas ligand), which induces death or deactivates invading lymphocytes by binding to CD95.^{35,36}

This system that protects the eye can become dysfunctional when expressed in other sites of the body. The most notable site is in tumors. Fas ligand expression has been seen in colon, gastric, breast, melanoma, pancreatic, ovarian, astrocytomas, lung cancer, and hepatocellular carcinoma.³⁷⁻⁴⁶ The cancers in question secrete or have present on their surface CD95L, which induces death for infiltrating immune cells. This has been correlated with T cell death and inactivation and results in rapid growth of the tumor and metastasis as it induces immune privilege for the tumor.

In our patient population, there was a greater percentage of cells that expressed the CD95 antigen as

well as greater numbers of antigens per cell. These results were rapidly reversed within 3 months after bariatric surgery in both the T lymphocytes and the neutrophils. We believe this over-expression places the lymphocytes at greater risk for cell death by tumor cells, which are prone to secreting fas ligand. This fact helps explain the higher mortality rate experienced by the morbidly obese for the same cancers that afflict the non-obese.⁴⁷⁻⁴⁹ Indeed the most frequent tumors suffered by the morbidly obese are the ones known to secrete Fas ligand.^{38,40-42,44-46} We hypothesize that the higher rates of colon, post-menopausal breast, prostate, biliary duct, endometrium, ovary, pancreas and gastric cancer suffered by the morbidly obese⁵⁰⁻⁵¹ result from over-expression of the CD95 antigen on the surface of lymphocytes, which in turn allows induction of immune privilege more easily than in a non-obese population. The abnormal expression of CD95 is reversed with bariatric surgical weight loss.

The limitations of this study would include a diversity of diseases and medications affecting our patient population. However, since obesity is intimately tied to related comorbidities, it is impossible to select a "healthy" cohort of obese patients. We did analyze patients by disease process and by medications and found no statistically significant differences between diabetes and medication use and morbidly obese patients who did not take medications or who were not diabetic. All morbidly obese patients responded similarly to gastric bypass, whether they were on medications or had diabetes.

Conclusion

We continue to present evidence for a chronic inflammatory state in morbid obesity and show how chronic inflammation results in immune-privileged sites in morbid obesity. Specifically, depression of CD62L suggests a functional decrease in the ability of lymphocytes to migrate and recirculate to sites of infection, inflammation and tumors in obesity. Additionally, the chronic inflammation of obesity causes higher levels of CD95 expression on PMNs and lymphocytes. This places immune cells at higher risk of cell death especially when confronted with inflammation from infection or Fas ligand expres-

sion from tumors. Indeed, if the hypothesis of increased immune privilege in morbid obesity is correct, then infection and tumor formation are part of the same pathological process. Currently, only surgery has been shown to correct this process.

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