

PAPER

Acute-phase response and immunological markers in morbid obese patients and patients following adjustable gastric banding

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OBJECTIVE: We measured markers of acute-phase response and immunological markers in morbid obese patients and in formerly morbid obese patients after a massive weight loss following adjustable gastric banding (GB).

SUBJECTS: A total of 49 morbid obese female patients with a body mass index (BMI) above 40 kg/m² were investigated during a study period of 6 months. Of these, 24 patients received a gastric banding (GB) and lost a minimum of 20 kg in 1 y (GB group) and 25 patients maintained their weight (obese group). In sum, 13 normal weight subjects (BMI < 24 kg/m²) were taken for controls.

METHOD: Plasma concentration of the acute-phase proteins, C-reactive protein (CRP), orosomucoid, complement factors C3 and C4 and white blood cell count, lymphocyte subsets and serum immunoglobulins were analyzed.

RESULTS: Acute-phase proteins were significantly lower in GB compared to morbid obese patients and remained significantly elevated in GB compared to controls. In addition, leukocytes, polymorphonuclear leukocytes and lymphocytes were significantly lower after GB and reached levels comparable to controls (except PMN). No difference in CD3 counts was observed in the three groups. CD4 increased and CD8 decreased in obese and GB patients when compared to controls whereas no statistical difference was found between obese and GB patients.

CONCLUSION: Our results confirm the positive effect of GB followed by a massive weight loss without apparent malnutrition. Subclinical chronic inflammation in morbid obese patients leads to irregularities in leukocyte and lymphocyte subsets. These alterations can be positively influenced by GB.

International Journal of Obesity (2003) 27, 355–361. doi:10.1038/sj.ijo.802240

Keywords: adjustable gastric banding; weight loss; inflammatory markers; acute-phase proteins; lymphocyte subsets

Introduction

Obesity and the metabolic syndrome are serious health problems as they are accompanied by cardiovascular risk factors such as dyslipidemia, hypertension, hyperinsulinemia and diabetes mellitus. The risk for premature atherosclerosis, cardiovascular disease and increased mortality can be correlated with body mass index (BMI) and is highest in morbid obese patients.^{1–3} In addition, morbid obesity (BMI above 40 kg/m²) without additional features of the metabolic

syndrome is an independent risk factor for coronary heart disease.⁴

Recently, there has been increasing interest in the inflammatory hypothesis as an underlying mechanism of arterial injury. Epidemiological data suggest a positive association of chronic subclinical inflammation and body weight.⁵ Elevation of C-reactive protein (CRP), a sensitive marker of inflammation, is frequently associated with increased BMI⁶ and predicts the development of diabetes mellitus.⁷

There are many potential reasons for the elevated CRP and acute-phase proteins including infection, neoplasm, inflammation or chronic heart disease.⁸ CRP, leukocytes, α -1-antitrypsin, orosomucoid and hemostatic factors were found to be elevated in obesity^{8,9} while an increase in the level of VLDL and decrease of HDL has been described.¹⁰

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Received 27 March 2002; revised 22 August 2002;

accepted 31 October 2002

Inflammatory cytokines are known to be operational in the induction of the acute-phase response. In type II diabetes and the metabolic syndrome plasma levels of the cytokines (interleukin (IL)-1 and IL-6), known to be mediators of acute-phase response, were increased.^{11,12}

Results from different studies suggest a correlation between chronic inflammatory response, obesity and endothelial dysfunction¹³ as well as a chronic alteration of the immune function. Elevation of CRP increased the risk for future myocardial infarction and stroke¹⁴⁻¹⁷ and has been reported with an increase of white blood count.¹⁸

To reverse or prevent the adverse health consequences, obese individuals are encouraged to lose weight. Despite the benefits of weight loss, there is increasing concern that massive dieting itself might be detrimental to health.¹⁹⁻²¹ Today bariatric surgery is a proven method of achieving long-term weight control for morbid obese patients. These operations were adapted, and today vertical banded gastroplasty (VBG) and adjustable gastric banding (GB) are regarded as effective techniques in bariatric surgery. A GB creates an early sense of satiety after eating and has no adverse effect on gastric function.²²⁻²⁴ Moreover, this method offers the advantage of a minimal-invasive (laparoscopic) approach.²⁵

Studies on the effect of weight loss on the acute-phase reaction and on changes of white blood cell count have mostly been conducted in moderately obese patients during a short dietary period on a very low calorie diet (VLCD).²⁶⁻²⁹

Therefore, the purpose of our study was to evaluate the effect of massive weight loss on markers of the acute-phase response and on lymphocyte phenotypes in morbid obese female patients following GB.

Subjects and methods

Patients

In total, 49 morbid obese patients were included over a period of 6 months in the study. Of these, 25 morbid obese female patients (41.96 ± 1.84 y) with a primary BMI above 40 kg/m^2 (obese group) and 24 formerly morbid obese patients (GB group) with a mean age of 38.75 ± 2.65 y were investigated when they were referred to our Nutrition Outpatient Department. A total of 13 normal weight subjects ($\text{BMI} < 24 \text{ kg/m}^2$) were included as controls. All morbid obese patients (with overweight longer than 5 y) were offered conventional lifestyle modification or bariatric surgery for choice. Obese patients who had no surgery and whose weight remained stable (± 5 kg) for 1 y were included (obese group). Patients of the GB group fulfilled the criteria for surgical treatment according to the American Bariatric Surgery Association³⁰ and received an adjustable GB (Lap-Band[®], BioEnterics, Carpinteria, CA, USA) at least 1 y ago. According to standardised inclusion criteria (30), only patients with a BMI higher than 40 kg/m^2 were considered for operation. No postoperative complications were observed in all of the GB patients. These patients were seen every 3

months after the operation and the medium time of follow-up was 15.9 ± 7.01 months. During these visits, in addition to routine blood checks (complete blood count, blood glucose, liver and renal function, lipids and CRP), vitamin and mineral serum levels (vitamin B₁₂ and folic acid, iron, zinc, magnesium and calcium) were measured and regular dietary advice was given. The nutrition management that we used has also been previously described.³¹ The day after the operation, patients were instructed to follow a liquid diet for 4 weeks. Thereafter a solid low-fat diet was given and a list of rules developed for patients with GB. However, the energy intake could vary between individuals, depending on the compliance and on band calibration. Band adjustments were only performed in the case of weight stabilisation (less than 4 kg in the last months) and a low vomiting frequency. As all patients with GB lost more than 20 kg during 1 y of the follow-up period, the excess weight loss (EWL%) demonstrated a good result of GB.

In all patients acute-phase proteins and leukocyte subsets were measured; in the GB group results from eight of 24 patients were available before and after surgery and compared with 13 controls. All relevant clinical details were obtained during routine visits. Subjects with manifested metabolic syndrome, for example, diabetes mellitus, were excluded.

Subjects suffering from infections or severe concomitant diseases, such as acute or chronic heart disease, apoplectic insult, urogenital and gynecological infections, hyper- or hypothyroidism, rheumatoid arthritis, any other primary or secondary immune deficiency, malignancy or impairment of liver and renal function or pregnancy were also excluded from the study (Figure 1).

The Institutional Review Board approved the study. Written informed consent was obtained from each patient.

Methods

Each patient had their body weight (to the nearest 0.1 kg) and height (to the nearest 0.1 cm) recorded while wearing light indoor clothes and no shoes. BMI was calculated as weight divided by height squared (kilograms per square meter).

Venous blood was drawn after a minimum of 8 h overnight fasting. Routine blood checks, minerals, vitamin B₁₂ and folic acid were directly sent to an approved laboratory and measured with standard techniques with internal and external quality control. CRP, white blood count, lymphocyte subsets, acute-phase response proteins including complement factors C3 and C4, and serum immunoglobulin levels were measured with standard nephelometric techniques.

Statistics

All continuous variables were expressed as mean \pm s.d., as otherwise reported. Statistical analyses of differences were

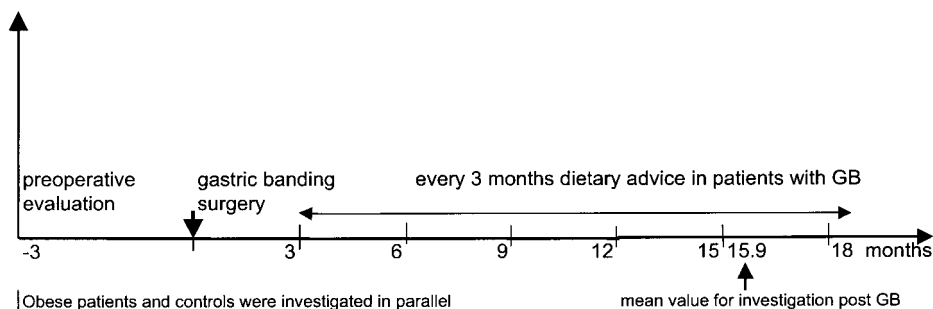


Figure 1 Study design for the evaluation of acute-phase proteins and lymphocyte subsets in obese patients and patients after adjustable GB, including a timetable for follow-up in GB.

performed using a one-way ANOVA to evaluate the effects of obesity and GB in the three groups. Significance was measured using the Mann-Whitney U-test for the exact *P* values. Differences were considered to be statistically significant at *P* values below 0.05.

Results

Patients

Clinical and biochemical characteristics of the three groups (obese, GB and controls) were summarized in Table 1. Subjects with GB had 137.97 ± 31.59 kg before the operation and reduced 44.29 ± 21.02 kg of their body weight over 15.95 ± 7.01 months. Their BMI was 50.12 ± 10.10 kg/m² before and 34.45 ± 7.11 kg/m² after the operation. The EWL was $65.01 \pm 23.01\%$ (range 38.2–110.2%). The mean BMI in obese and control subjects stayed unchanged over the study period (43.20 ± 5.59 vs 21.15 ± 2.18 kg/m²). The patients were comparable in age, glucose and cholesterol levels. Obese patients had lower HDL cholesterol compared to both GB (49.90 ± 14.20 and 55.30 ± 21.00 mg/dl) and normal-weight subjects (64.30 ± 34.70 mg/dl), but the difference was only statistically significant when compared to controls (*P* = 0.04). Obese and GB subjects had significantly higher

levels of triglycerides in comparison to controls (141.00 ± 58.50 and 119.00 ± 45.00 mg/dl vs 84.00 ± 29.90 mg/dl, *P* = 0.008 and 0.004), whereas triglyceride values were comparable (*P* = 0.32) in obese and GB subjects.

Serum total protein, vitamin B₁₂, folic acid, calcium, zinc and magnesium levels were comparable before and after GB and were within normal ranges (Table 2).

Acute-phase proteins

CRP and orosomucoid as well as the complement components C3 and C4 are significantly higher in obese individuals compared to GB and controls. A significant decrease in CRP (1.2 ± 0.8 vs 0.85 ± 0.69 mg/dl, *P* = 0.02), orosomucoid (106.48 ± 17.03 vs 80.54 ± 23.19 mg/dl, *P* < 0.0001) and C3 (155.00 ± 21.5 vs 131.75 ± 28.33 mg/dl, *P* = 0.0009) has been observed after GB as compared to the obese. A slight decrease in C4 (34.64 ± 9.6 vs 29.9 ± 6.73 mg/dl, *P* = 0.05) was also seen. All parameters remained elevated in the GB group as compared with controls (Table 3).

The number of leukocytes after GB was significantly lower than in the obese (5670.83 ± 1092.46 vs 7727.27 ± 1654.78 mg/dl, *P* < 0.0001) and comparable to the leukocyte counts in the healthy individuals (5388.89 ± 1306.18 mg/dl). Polymorphonuclear leukocytes (PMN) were also significantly higher in the obese (4089.21 ± 1244.67 mg/dl) compared to GB (3154.35 ± 831.14 mg/dl, *P* = 0.004) and controls (2488.44 ± 632.64 mg/dl, *P* < 0.0001). In GB PMN levels remained significantly elevated to the control group (Table 4).

Table 1 Clinical characteristics of subjects

	Obese	GB	Controls
Age (y)	$39.8 \pm 6.6^{***}$	39.7 ± 9.1	31.8 ± 8.1
Weight (kg)	$116.0 \pm 13.8^{***,***}$	93.6 ± 21.3	59.5 ± 7.5
BMI (kg/m ²)	$43.2 \pm 5.6^{***,***}$	34.5 ± 7.1	21.2 ± 2.2
Fasting plasma glucose (mg/dl)	83.4 ± 12.9	88.3 ± 21.1	92.1 ± 2.2
Fasting cholesterol (mg/dl)	196.0 ± 25.4	208.8 ± 41.0	194.8 ± 13.4
HDL (mg/dl)	$49.9 \pm 14.2^*$	55.3 ± 21.0	64.3 ± 34.7
LDL (mg/dl)	141.0 ± 58.5	119.3 ± 45.0	112.4 ± 35.6
Triglycerides (mg/dl)	$141.0 \pm 58.5^{**}$	119.0 ± 45.0	84.0 ± 29.9

**P* < 0.05 obese vs controls.

***P* < 0.05 GB vs controls.

****P* < 0.05 obese vs GB.

Table 2 Serum total protein, vitamins and minerals before and 15.9 months after GB within the normal range (mean ± s.d.) Differences NS

	GB before	GB after 15.9 months	Normal range
Total protein (g/dl)	7.1 ± 0.45	6.7 ± 0.04	4.6–8.7
Iron (μg/dl)	61.5 ± 24.02	50.2 ± 1.57	49–151
Ca (mmol/l)	2.3 ± 0.20	2.3 ± 0.01	2.00–2.62
Zinc (μg/dl)	94.0 ± 15.74	92.3 ± 10.82	70–114
Vit. B ₁₂ (pg/ml)	352.7 ± 251.47	365.7 ± 10.65	187–1059
Folic acid (ng/ml)	6.35 ± 2.25	7.62 ± 0.22	5.3–14.2

Table 3 Acute-phase proteins in obese, GB and control subjects

	Obese	GB	Control
CRP (mg/dl)	1.20 ± 0.14 ^{*,**}	0.85 ± 0.14 ^{****}	0.40 ± 0.04
Orosomucoid (mg/dl)	106.48 ± 4.83 ^{*,**}	80.54 ± 4.73 ^{*****}	63.67 ± 4.83
C3 (mg/dl)	155.00 ± 3.74 ^{*,**}	131.75 ± 5.78 ^{*****}	108.11 ± 5.01
C4 (mg/dl)	34.64 ± 1.67 ^{*,**}	29.92 ± 1.37 ^{****}	21.00 ± 2.13

P* < 0.05 obese vs GB.*P* < 0.0001 obese vs GB, obese vs control.****P* = 0.0009 obese vs GB.*****P* < 0.01 GB vs control.******P* < 0.05 GB vs control.

These results were almost confirmed in a subgroup of eight patients of the GB group when measured before and after surgery and compared with controls at the beginning and 6 months after the study (Table 5). All acute-phase proteins were significantly higher before GB and were still elevated when compared to control levels.

Serum concentration of immunoglobulins and immunoglobulin subsets did not differ significantly between the three study groups (Table 4).

Lymphocyte subsets

Lymphocytes decreased significantly after GB compared to obese subjects (2236.48 ± 519.13 vs 3206.70 ± 888.36 mg/dl, *P* < 0.0001) and reached control levels. The percentage of lymphocyte subset CD3 did not differ in the three groups (74.91 ± 5.36 vs 72.13 ± 8.57 vs 70.11 ± 7.54%, *P* > 0.05), whereas the percentage of CD4 counts was higher in the obese (52.15 ± 6.55%, *P* < 0.0001) and GB group

(51.46 ± 6.27%, *P* = 0.0002) than in control subjects (41.56 ± 4.42%). CD8 counts were lower in the obese and GB groups (29.21 ± 5.74 vs 28.04 ± 5.15%, *P* = 0.006 and 0.002, respectively) than in control subjects (34.56 ± 4.45%; Table 4).

Discussion

This study examined the role of obesity in the enhancement of acute-phase response and alterations of immunological markers. We compared morbid obese patients, patients after adjustable GB and a subgroup before and after GB.

In order to have a population as homogeneous as possible, only female individuals without features of the metabolic syndrome (except hypertriglyceridemia) were included in our study. In addition, we excluded a wide variety of acute and chronic diseases,³² which have been known to increase CRP serum levels and several other acute-phase proteins over a long period of time. The massive weight loss after GB is not followed by apparent malnutrition or by vitamin and/or mineral deficiencies. This procedure and a proper, regular follow-up by a multidisciplinary management team excluded other stimuli on immunological markers.

The results of this study confirmed the well-known elevation of acute-phase proteins including CRP and leukocytosis in morbid obese female patients, which may be indicative for subclinical chronic inflammation associated with an increased risk for cardiovascular diseases.^{13–18} The levels of acute-phase proteins were dramatically higher in morbid obese patients compared to patients following massive weight loss after GB.

Table 4 White blood cell count, lymphocyte subsets and immunoglobulins in obese, GB and controls

	Obese	GB	Controls
Leukocytes (mg/dl)	7727.27 ± 1654.78 [*]	5670.83 ± 1092.46	5388.89 ± 1306.18 ^{*****}
PMN (mg/dl)	4089.21 ± 1244.67 ^{**}	3154.35 ± 831.14 ^{***}	2488.44 ± 632.64 ^{*****}
Lymphocytes (mg/dl)	3206.70 ± 888.36 [*]	2236.48 ± 519.13	2611.33 ± 753.1 ^{*****}
CD 3 (%)	74.91 ± 5.36	72.13 ± 8.57	70.11 ± 7.54
CD 4 (%)	52.15 ± 6.55	51.46 ± 6.27 ^{****}	41.56 ± 4.42 ^{*****}
CD 8 (%)	29.21 ± 5.74	28.04 ± 5.15 ^{****}	34.56 ± 4.45 ^{*****}
IgG (mg/dl)	1100.96 ± 174.86	1094.63 ± 233.58	1082.22 ± 282.32
IgG1 (mg/dl)	611.8 ± 145.6	551.75 ± 127.01	618.33 ± 252.03
IgG2 (mg/dl)	347.96 ± 119.76	400.06 ± 136.66	375.0 ± 121.63
IgG3 (mg/dl)	50.28 ± 22.16	46.94 ± 14.05	40.33 ± 13.21
IgG4 (mg/dl)	41.52 ± 25.22	45.38 ± 46.97	59.78 ± 39.13
IgA (mg/dl)	294.24 ± 198.74	261.38 ± 140.74	236.67 ± 75.91
IgM (mg/dl)	207.96 ± 134.29	190.5 ± 57.01	231.67 ± 64.38

P* < 0.0001 obese vs GB.*P* = 0.004 obese vs GB.****P* = 0.02 GB vs control.*****P* < 0.005 GB vs control.******P* = 0.0002 obese vs control.******P* < 0.0001 obese vs control.******P* = 0.04 obese vs control.******P* = 0.006 obese vs control.

Table 5 Acute-phase proteins and white cell blood count in a subgroup in GB and control patients compared before and after

	Pre-GB	Post-GB	Precontrol	Postcontrol
CRP (mg/dl)	1.35 ± 0.78*	0.69 ± 0.51	0.35 ± 0.02	0.31 ± 0.29
Orsomucoid (mg/dl)	111.63 ± 15.47**	84.75 ± 16.73	79.31 ± 17.45	85.31 ± 22.71
C3 (mg/dl)	159.63 ± 19.26****	125.63 ± 32.56	115.0 ± 16.66	129.15 ± 13.27
C4 (mg/dl)	32.88 ± 5.99	29.75 ± 5.37	26.1 ± 8.1***	33.85 ± 10.07
Leukocytes (/cmm)	7975.0 ± 1601.56**	5912.5 ± 832.27	7645.45 ± 2544.55	7572.73 ± 3520.82
PMN (/cmm)	4474.0 ± 960.5**	3281.25 ± 707.58	4827.18 ± 1717.56	4852.27 ± 2615.87
Lymphocytes (/cmm)	3006.4 ± 1034.1*	2284.38 ± 428.67	2368.00 ± 833.33	2314.09 ± 1036.6

* $P < 0.05$ pre-GB vs post-GB.

** $P < 0.01$ pre-GB vs post-GB.

*** $P < 0.05$ precontrol vs postcontrol.

**** $P < 0.009$ pre-GB vs post-GB.

We measured the concentration of additional other acute-phase proteins: orosomucoid and the complement factors C3 and C4, normally associated with an elevation of CRP. All acute-phase proteins were significantly increased in obese (and GB) patients compared to normal-weight individuals, reflecting the correlation of acute-phase proteins with BMI levels.⁶

We enumerated white blood cells and our results confirmed leukocytosis in obese patients, which has been described before.^{18,25,26} The results of the currently available research in obesity indicate an elevation of differential white blood cell count, including leukocytosis and an alteration of lymphocyte phenotypes.³² In our study the numbers of both, PMN and lymphocytes, were significantly elevated in morbid obese patients.

Nieman²⁹ found an elevation of leukocytes and lymphocytes with a significant decrease of white blood cell count, except for CD4 and CD8 subsets, following weight loss during a VLCD in moderately obese patients (BMI 33.2 ± 6.5 kg/m²). Chandra and Kutty³⁴ did not find any changes in numbers of T and B lymphocytes, immunoglobulins and complement components.

Although obese individuals are encouraged to lose weight in order to reverse or prevent the adverse health consequences of obesity, only a small number of studies examined the effect of weight reduction strategies on acute-phase proteins and immunological alterations. Particularly important in the discussion of obesity therapy and immune function is the type and duration of diet. Imbalance of diet composition can alter immunocompetence. For example, proteins, especially essential amino acids, iron or folic acid, are important for the maintenance of immune function.^{35,36} Still only a few studies investigated the prevalence of deficiencies of nutrients in obesity, probably because overnutrition is claimed to be the main cause of obesity. Comparison of published data is complicated because various dietary regimens are often applied, which might be followed by different degrees of malnutrition.

Most studies were conducted in moderately obese female and male subjects using VLCD and only over a short diet period. This diet provides an adequate intake of macro- and

micronutrients so that in these studies impairment of the immune function might not be a result of nutrient deficiencies.

In morbid obese patients, studies with gastric-restrictive procedures were mostly performed resulting in malabsorption and micronutrient deficiencies, such as zinc or iron, that could lead to impaired immunity.³⁶ We measured serum protein, iron, vitamin B₁₂ and folic acids and found no significant differences in the blood concentrations before and after GB.

As apparent malnutrition is not a consequence of GB,²³ this surgical procedure seems to be a good model for studying the consequences of massive weight loss in morbid obese patients. Although data of only eight patients before and after GB were available, the comparison of the obese and the GB group confirmed these results.

Field *et al*²⁶ presented the results of 12 healthy obese female and male subjects after 6 weeks VLCD and 2 weeks of usual diet with an average weight loss of 13 kg. They found a decrease in the numbers of total leukocytes, PMN, lymphocytes and monocytes over the diet period. Total numbers of white blood cell count and lymphocytes returned to baseline levels. Analysis of lymphocyte subsets revealed a significant decrease in the percentage of CD4 cells but no change in the number of CD8 cells. Tanaka *et al*²⁸ found an impaired CD4- and CD8 function, and Scanga *et al*³⁷ reported a significant decrease in peripheral blood leukocytes and lymphocytes and an unchanged CD56 proportion after a weight loss of about 10%.

In accordance with other publications, we confirmed the association of obesity with significantly higher leukocyte subsets, but no discernible alterations in lymphocyte phenotypes.^{25,28} Our study presents results in morbid obese and GB patients after massive weight loss and a long treatment period of 15.95 ± 7.01 months after the surgery procedure. Morbid obese subjects are of enormous clinical interest because all conservative treatments, including drugs, have failed to achieve long-term weight loss.

The total number of leukocytes after GB was significantly lower than in the obese and comparable to the leukocyte counts of normal-weight individuals. PMN were significantly

higher in the obese compared to GB and controls. The serum levels of PMN in GB were still significantly elevated compared to control levels. These results were confirmed in a subgroup of GB patients before and 12 months after GB.

Studies on immunological alteration in anorexia nervosa have provided additional information on the immunological consequences of long-term caloric deficits and large weight loss. These individuals, although they become extremely emaciated, are reputed to have adequate intakes of protein, fat and micronutrients.^{38,39} This permits the comparison with weight loss after GB. In anorexia nervosa the status of immune function seems to depend on the degree of weight loss, as notifiable impairment of lymphocyte function is only seen as subjects become severely anorectic (below 60% of the desirable weight).^{40,41}

Fink *et al*⁴² observed normal CD4 counts in anorexic and obese patients before and after VLCD diet, and enumerated only low CD8 counts in anorexic and obese patients after weight loss, but not before.

Our analysis confirmed higher levels of lymphocytes and irregularities of lymphocyte subsets in morbid obese patients. In GB lymphocyte counts were comparable to control levels.

The percentage of CD3 counts did not differ significantly in the three groups. CD4 levels (in percent) were significantly higher in obese and GB subjects. CD8 counts in percent were lower in obese and GB when compared to control subjects.

No significant differences in the levels of immunoglobulin classes IgG, IgA and IgM were found in our morbid nondiabetic obese patients. Recently, higher levels of gamma globulin concentration to be related to higher BMI were reported and predict diabetes mellitus in Pima Indians.⁶ These different results may reflect genetic differences in Pima and Caucasians.⁴³

The question as to whether the difference observed between the morbid obese and the group after massive weight loss (GB group) was because of the weight loss *per se* or arose because of negative energy balance cannot be answered with certainty. However, all changes observed brought values closer to values obtained in the nonobese. We would therefore favor the explanation of absolute weight loss as the likely reason. Studies assessing these variables after weight loss ended and weight has stabilized for a longer period of time will be needed for clarification.

In conclusion, these results add to the body of evidence of relations between massive obesity, BMI levels and an increase of acute-phase reactants, including CRP levels. This chronic subclinical inflammation also includes irregularities of granulocyte and lymphocyte subsets. These alterations can be positively influenced by massive weight loss following GB without apparent malnutrition. Still more research is needed to evaluate if massive weight loss without apparent malnutrition may reduce the risk for cardiovascular diseases by reducing chronic subclinical inflammation.

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