

# Alteration of Immune System after Bariatric Surgery: A Systematic Review

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## ABSTRACT

**Background:** It is well established that there is a significant correlation between overweight/obesity and immune system function. However, it is not clear how the weight loss after bariatric surgery would affect the function of the human immune system.

**Objectives:** We aimed to conduct this systematic review to assess the current knowledge on alteration of immune system after bariatric surgery.

**Methods:** We reviewed all potentially related articles published between January 2006 and September 2020 to review the obesity surgery literature and immune system activity in Medline/PubMed.

**Results:** The results of a review of studies showed that obesity is associated with a low-grade systemic inflammatory condition in which innate and adaptive immune cells increase the secretion of proinflammatory cytokines. Weight loss due to bariatric surgery leads to significant changes in adaptive immune cells. The number of CD4 + and CD8 + T cells decreases. Decreased Th1/Th2 ratio also occurs after weight loss due to obesity surgery. Also, the ratio of inflammatory and anti-inflammatory cytokines changes following change in immune cells ratio.

**Conclusion:** Weight loss following obesity surgery results in anti-inflammatory status, which occurs with obesity.

**Keywords:** Immune system; Bariatric surgery; Innate immunity; Adaptive immunity

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**INTRODUCTION**

Obesity is defined as excess body fat. Body mass index (BMI) has been the most widely used parameter for assessing and classifying obesity. The World Health Organization defines obesity BMI as "equal to or greater than 30 Kg/m<sup>2</sup>". The prevalence of obesity has increased alarmingly in recent decades. One the growing worldwide health concern is severe obesity which has high mortality and costs for the public health care systems, while weight loss results in improvement of its complications. The global prevalence of severe obesity is higher in women than in men, and in 2020, according to the World Health Organization, the prevalence of severe obesity was reported 11.5% in women and 6.9% in men. Obesity has been associated with metabolic disorders such as insulin resistance, dyslipidaemia, and non-alcoholic fatty liver disease, and with endocrine diseases such as type 2 diabetes (T2DM), polycystic ovary syndrome, and vitamin D deficiency.<sup>1</sup> Despite a strong epidemiological link that indicates an increased risk of obesity in people with metabolic diseases, it should be noted that some obese people have no obvious disorders. Obesity has also been linked to autoimmune diseases such as rheumatoid arthritis, psoriasis, and systemic lupus erythematosus. In addition, obesity increases mortality and reduces the quality of life.

There is some weight-loss methods for any stage of overweight including calorie-restricted diet, exercise, life style modification and surgery. In severe obesity, surgery is a proper method for stable weight-loss. Bariatric surgery is considered to be the most effective long-term treatment for obesity. According to the clinical guidelines of the American Society for Metabolic Surgery and Obesity, surgical methods are suitable for weight loss of patients with a BMI>40 kg/m<sup>2</sup>, BMI>35 kg/m<sup>2</sup> with at least one disease associated with obesity or BMI>30 kg/m<sup>2</sup> for patients with T2DM or metabolic syndrome. Surgical procedures base are food intake restriction, malabsorption, or both. Limiting surgeries include Laparoscopic Adjustable Gastric Band (LAGB), Vertical Banded Gastroplasty (VBG), and Sleeve Gastrectomy (SG). Absorption-related surgeries include Jejunioileal Bypass (JIB), Biliary and Pancreatic Diversion Bilipancreatic (BPD), and Biliary and Pancreatic Diversion by Bilipancreatic Diversion with Duodenal Swit These two methods (RYGB) is Roux-en-Y gastric bypass. Patients after obesity surgery should be under the constant supervision of the medical team to prevent short-term and long-term complications related to

surgery, and the success rate of the patient depends on his long-term follow-up after surgery.<sup>2</sup> Obesity surgery can also lead to complications, including complications during surgery (trocar injuries, spleen injury, and portal vein injury), early postoperative complications (bleeding, wound infection, anastomotic leakage, embolism, pulmonary embolism, and cardiopulmonary complications) and late postoperative complications (gallstones, nutritional deficiencies, and neuropsychological complications).

**LITERATURE REVIEW**

Obesity is considered a low-grade inflammatory condition characterized by an increase in acute phase reactants and pro-inflammatory cytokines. Inflammation is driven by the immune response, which is divided into innate and adaptive immunity. The innate immune response is nonspecific and rapid, mediated by neutrophils and macrophages that rapidly migrate to inflamed tissues to try to kill the attacker. On the other hand, the adaptive immune response against a pathogen is mediated by T and B lymphocytes, which detect specific high-affinity epitopes by T cell receptor (TCR) or antibody production, respectively. Both responses usually interact and amplify each other and have a synergistic effect, as do macrophages that act as antigen-presenting cells (APCs) for T cells, which in turn secrete proinflammatory cytokines such as interferon- $\gamma$ , which activates macrophages more.

The obesity-related pro-inflammatory environment is driven in part by adipose tissue macrophages, which are part of the innate immune system. However, recent studies show that compatible immune cells, such as T and B lymphocytes, play a key role in activating and maintaining such inflammation. The purpose of this study is to highlight the changes in the adaptive immune system that follow weight loss due to bariatric surgery.

We reviewed all potentially related articles published between January 2006 and September 2020 to review the obesity surgery literature and immune system activity. 2006 was chosen as the starting date because it was the first article in the text review to be found in the initial search. The terms immunity, immune cells, innate immunity, acquired immunity, obesity surgery, RYGB, LAGB, VBG, SG, JIB and BPD were used to search PubMed. Finally, fifteen articles included in present systematic review study.

**DISCUSSION**

Changes in the number of lymphocytes and changes in phenotype as well as the secretion of their by-products after weight loss due to bariatric surgery have been reported. Some studies have shown that shortly after gastric banding, the Th1/Th2 ratio decreases with Th1, and Th2 levels may also increase, which has been reported in patients with T2DM and pre-diabetes, with improvements in glucose metabolism. B lymphocytes have also been shown to change from an effector to a regulatory phenotype, altering the secretion of pro-inflammatory cytokines by T lymphocytes after RYGB.<sup>3</sup> In addition, studies have shown that the total number of circulating CD4 + and CD8 T cells decreases after further laparoscopic curvature in obese patients, indicating a decrease in cell-mediated level of immune activity. Similarly, a decrease in the number of B, T CD8 + and natural killer (NK) lymphocytes after obesity surgery has been described in some severely obese people with insulin resistance. However, in a study with a small statistical population consisting of 20 severely obese women, no significant change was observed in the sub-populations of T CD4 +, T CD8 +, B and NK after obesity surgery. When analyzed by type of surgery, changes in CD4 + T lymphocytes were associated with changes in BMI in the RYGB subgroup, but not in the LAGB group, suggesting that more pronounced weight loss may be associated with a decrease in CD4 T cells. Be. Alternatively, four months after further laparoscopic curvature, CD4 + T cells decreased from 38.2% to 29.3%, CD8 + cells from 17.3% to 9.5%, and leptin levels from 43.01 to 24.8 ng/ml in 20 patients. However, the association between the changes observed in the lymphocyte and leptin populations in the study was not evaluated. With these results in mind, after performing various surgical procedures for obesity, weight-dependent decrease in lymphocyte differentiation of the inflammatory phenotype occurs.

In addition, Tfh cells, which have a potential role in the activation and differentiation of B lymphocytes, have been shown to reduce the expression of activating markers and the secretion of pro-inflammatory cytokines after RYGB. It has also been reported that Tfh cell activation markers are incorrectly regulated 3 months after RYGB.<sup>4</sup> Also, the secretion of IFN- $\gamma$ , IL-2, IL-4, and IL-17 by Tfh cells was shown to be reduced, while no significant change in IL-10 was observed. IL-10 secretion was described after 72 h of incubation of autologous enterotoxin B- (SEB-) B cells pulsed with Tfh post-

RYGB plus staphylococcus plus higher staphylococci compared to Tfh B cells before RYGB plus cells. In addition, Tfh IL-10 + was shown to differentiate naive B cells into an IL-10- and TGF- $\beta$ -secreting phenotype that is directly mediated by IL-10 itself. Isolated B cells after RYGB had higher expression of IL-10 and TGF- $\beta$ . These findings indicate a general decrease in inflammatory cytokines and an overall increase in anti-inflammatory cytokines secreted by Tfh cells, which may have a direct effect on the differentiation of anti-inflammatory B cells. Similarly, in another study, 3 months after RYGB, it was found that B lymphocytes change from a pro-inflammatory IL-6 + phenotype to an anti-inflammatory IL-10 + phenotype, while it has been shown that T lymphocytes reduce the secretion of pro-inflammatory cytokines IL-17 and IFN- $\gamma$ . In addition, B and T cell cocultivation showed that preoperative B cells stimulated the secretion of pro-inflammatory cytokines by T cells, whereas postoperative B cells inhibited the secretion of pro-inflammatory cytokines. They pay. These findings suggest that obesity surgery causes changes in the pro-inflammatory to anti-inflammatory lymphocyte phenotype that further affect other cell cells to regulate their inflammatory potential.

In another study, researchers reported the results of an inflammatory condition in obese and diabetic women 3 months after RYGB. They showed that weight loss leads to a decrease in systemic CRP, total T cells, and helper T cells, meanwhile, paradoxically, also increases a systemic concentration of TNF- $\alpha$ . It is speculated that this subsequent finding may indicate incomplete recovery from surgery, and longer follow-up periods are recommended to achieve a better picture of systemic inflammation after bariatric surgery. In addition, a decrease in the number of circulating mucosal-associated invariant T or MAIT cells was observed with a surprising increase in pro-inflammatory IL-17 secretion in obese individuals compared with healthy individuals. Fewer MAIT cells in obese individuals have been attributed to increased activation and penetration of adipose tissue.

After bariatric surgery, individuals were reported to increase the number of MAIT cells in the peripheral blood, but without decreasing IL-17 secretion. The relationship between changes in MAIT cells and whether they reflect a reduction in their pro-inflammatory phenotype needs further study.

**CONCLUSION**

The results of a review of studies showed that obesity is associated with a low-grade systemic inflammatory condition in which innate and adaptive immune cells increase the secretion of pro-inflammatory cytokines. The potential mechanism of this phenomenon is a stable inflammatory environment in obese conditions that leads to insulin resistance and metabolic diseases, and the improvement of these inflammatory conditions is achieved through weight loss. Obesity surgery is the most effective solution for significant and consistent weight loss known to date. Weight loss due to bariatric surgery leads to significant changes in adaptive immune cells. The number of CD4 + and CD8 + T cells decreases. Also, Tfh increases the secretion of anti-inflammatory cytokines and, as a result, leads to an increase in Breg cells. Anti-inflammatory cytokines, including IL-10 and TGF- $\beta$ , which are secreted by Breg cells, prevent the release of pro-inflammatory cytokines IFN- $\gamma$  and IL-17 by T cells.

Decreased Th1 / Th2 ratio also occurs after weight loss due to obesity surgery, which may be related to improved insulin sensitivity. After bariatric surgery, immune cells gain stronger antioxidant capacity and reduce the levels of fat and DNA oxidation products. Oxidative stress is a known modulator of lymphocyte differentiation, metabolism, and proliferation that improves after bariatric surgery. Changes in the availability of

metabolic substrates after bariatric surgery affect the adaptive immune response after bariatric surgery and still provide a field for further study. Mechanisms involved in obesity-induced changes in adaptive immunity include weight loss, calorie deficiency, insulin sensitivity, fatty acid, and changes in metabolite concentrations. A better basis for the specific effect of each of these mechanisms in modulating immune cells in the field of weight loss through obesity surgery in a patient with severe obesity represents an open field for study. Further research is focused on the interaction between the immune system pathways and metabolic processes after obesity surgery, which may lead to advances in the treatment of obesity and related diseases.

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