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Does bariatric surgery reduce inflammatory activation in obesity? Evidence by complement fraction C5a

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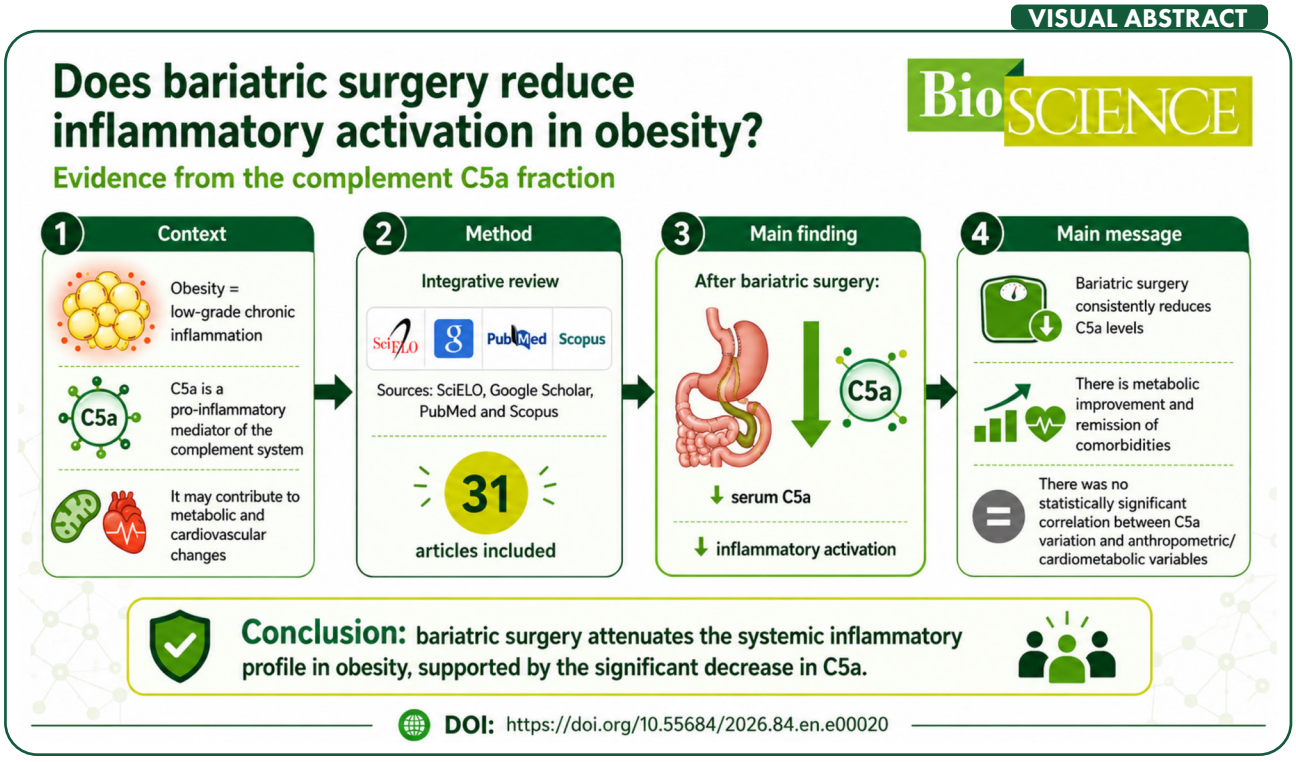
VISUAL ABSTRACT



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Central Message
Obesity is a state of chronic low-grade inflammation, which plays a central role in the genesis of several metabolic and cardiovascular comorbidities. Among the mediators of this process, the complement system stands out, whose activation contributes decisively to the perpetuation of the inflammatory response

Perspective
Serum pro-inflammatory C5a levels showed a significant and consistent reduction after the surgical intervention. Although there was a robust reduction in C5a associated with metabolic improvement, no statistically significant correlations were observed between C5a variation and anthropometric and cardiometabolic variables. However, bariatric surgery is effective in resolving comorbidities and reducing the systemic inflammatory profile, supported by the significant drop in C5a levels.

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ABSTRACT

Introduction: Obesity is a state of chronic low-grade inflammation, which plays a central role in the genesis of several metabolic and cardiovascular comorbidities. Among the mediators of this process, the complement system stands out, whose activation contributes decisively to the perpetuation of the inflammatory response.

Objective: To review the changes in the serum concentration of the C5a fraction of the complement system in obese patients undergoing Roux-en-Y gastric bypass, and to investigate their possible correlation with changes in metabolic parameters.

Method: Integrative review based on online search obtained through virtual platforms with a search for DECs descriptors "complement, C5a, obesity and inflammation" related to the theme, with AND or OR search, considering the title and/or abstract. The material for reading and analysis was selected from the SciELO, Google Scholar, Pubmed and Scopus platforms.

Result Considering only those that had a greater relationship with the theme, 31 articles were read in full. Conclusion: Bariatric surgery promotes a significant reduction in serum C5a levels, suggesting attenuation of inflammator

y activation mediated by the complement system.

KEYWORDS: Complement. C5a. Obesity. Inflammation.

INTRODUCTION

Obesity has become an epidemic that affects the entire society, imposing a significant burden on health systems and greatly increasing population morbidity and mortality. Currently, it is considered by the WHO (World Health Organization) as one of the main global risk factors in public health. This chronic condition is closely linked to the development of associated comorbidities, such as metabolic syndromes (type 2 diabetes mellitus and dyslipidemias), cardiovascular diseases, high risk of malignant neoplasms and arthropathies.[1,2] In addition to mechanical factors, it is characterized by a state of chronic low-grade inflammation driven by dysfunctional white adipose tissue (BAD) that acts as an active endocrine organ, increasing cardiovascular risk through the dysregulated secretion of adipokines and other signaling molecules.[3,4] In addition, macrophages infiltrate the BAD, which secrete pro-inflammatory cytokines (TNF-α, IL-6) and contribute to metabolic stress.[5]

The complement system is an essential component of innate immunity, consisting of a serial enzymatic cascade that aims at the removal of pathogens by lysis, opsonization and the elimination of cellular debris.[6] This mechanism has three activation pathways: the classical one, triggered mainly by antibodies; the lectin pathway, activated by microbial carbohydrates; and the alternative.[7,8] These pathways converge to the formation of C5 convertase, which culminates in the production of the membrane attack complex (C5-C9, or MAC) and the release of potent anaphylatoxins, such as C3a and C5a.[9] C5a is a key anaphylatoxin at the interlink between inflammation and metabolism. It acts through G-protein-coupled receptors (C5aR) and is a crucial element in the recruitment and activation of inflammatory cells and in the upregulation of adhesion molecules, favoring neutrophil-endothelial interactions.[5,8,10]

The link between obesity and complement is strengthened by complement factor D (adipsin). This factor, secreted by adipocytes among other cell types, is directly involved in the activation of the alternative pathway, playing a critical role in the production of C3a and C5a. Adipsin regulates adipose tissue homeostasis and has been associated with metabolic disorders, demonstrating a direct role of BAD in amplifying the complement inflammatory cascade.[11]

Bariatric surgery is a treatment option for severe obesity, promoting significant and sustained weight loss, with a consequent decrease in the incidence of associated diseases.[12,13] This intervention induces remarkable remission of the inflammatory process and substantial improvement in metabolic status.[5] However, the scientific literature is scarce in the detailed evaluation of the behavior of the C5a component in obese individuals and on the impact of weight loss induced by bariatric surgery in this context.[11]

It is in this gap that the present study is inserted, which aims to review the behavior of serum C5a levels in obese individuals undergoing bariatric procedures in Roux-en-Y bariatric procedures, its possible association with changes in the anthropometric and metabolic profile, adding information on the role of complement modulation in the postoperative response and in the improvement of comorbidities.[14,15]

METHOD

Integrative review made by collecting information for reading and analysis from online research on virtual platforms. Initially, a search was performed for DECs descriptors related to the theme, using the following terms: "complement, C5a, obesity and inflammation" with a search AND or OR, considering the title and/or abstract. The material for reading and analysis was selected from the SciELO, Google Scholar, Pubmed and Scopus platforms, and considering only those that were more related to the theme, the texts were read in full, including 31 articles in this review.

DISCUSSION

The official parameter for the determination and classification of obesity, already well known, is the Body Mass Index (BMI), calculated by the ratio between weight (kg) and the square of height (m^2) and defines obesity as grade I BMI between 30-34.[9] kg/m^2; grade II

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(severe) between 35-39.[9] kg/m², and grade III (morbid) BMI ≥ 40 kg/m². Although several predisposing factors contribute to obesity - including metabolic, hormonal, genetic and psychosocial factors - global rates continue to rise.[16,17] Many researchers consider obesity to be a multifactorial disease, in which, despite genetic inheritance, environmental factors such as the consumption of high-fat diets and a sedentary lifestyle play a critical role in increasing body fat levels and the risk of chronic diseases.[14] Type 2 diabetes mellitus (DM 2) is characterized by chronic hyperglycemia, resulting from insufficient insulin production or deficiency of cellular sensitivity to this hormone18,with obesity being the most significant risk factor in its development.[19] This risk is exacerbated by insulin resistance caused by increased adipocyte volume, especially in abdominal fat. In a scenario of insulin resistance, the anti-inflammatory mechanisms of insulin are compromised, favoring pro-inflammatory signaling.[20]

Adipokine and cytokine synthesis by adipose tissue

Adipose tissue is composed of adipocytes, cells primarily responsible for storing triglycerides, the body's main energy reserve. However, adipose tissue is metabolically active, exerting a vital endocrine function in the synthesis and secretion of various hormones and cytokines, collectively known as adipokines.[21]

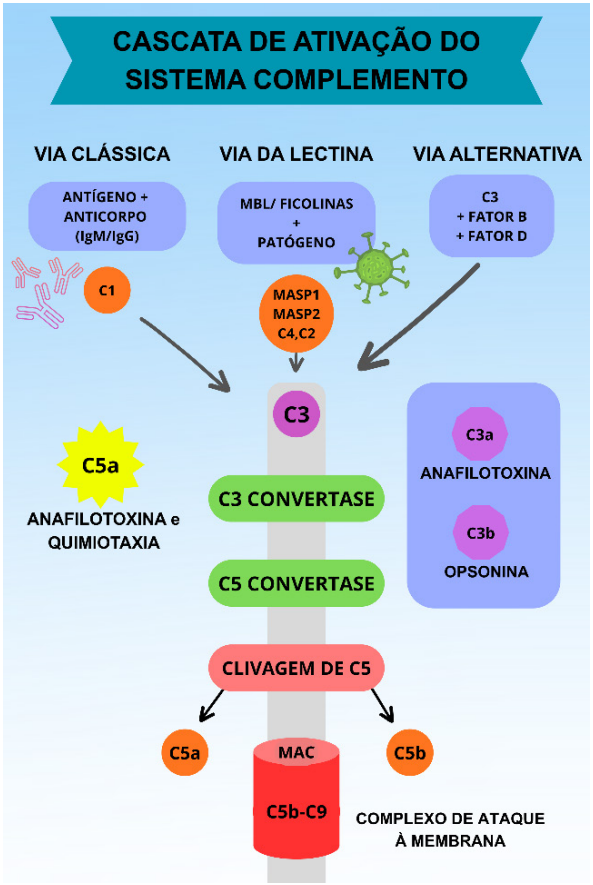
Resistin is a cytokine that modulates the action of insulin and glucose and lipid homeostasis. This adipokine contributes significantly to metabolic stress induced by positive caloric balance,5 also having pro-inflammatory properties and being secreted by adipocytes, monocytes, and macrophages.[22] Leptin and adiponectin are also adipokines that participate in energy regulation and inflammatory responses. Leptin regulates energy balance by promoting satiety via the hypothalamus. In obese individuals, the serum leptin concentration is elevated due to leptin resistance, caused by the increase in body fat percentage.[7] On the other hand, adiponectin acts as a cardiovascular protection factor and is an important anti-inflammatory protein. However, its synthesis is typically decreased in obese patients, increasing the risk of comorbidities.[5]

The complement system

The complement system, discovered by Jules Bordet in 1890, is a crucial mediator of the immune response, belonging to the innate immune system. Its main function is to complement the defense mechanisms against pathogens and promote the elimination of apoptotic cells and cellular debris, also influencing the adaptive response through opsonization and potentiation of the action of antibodies.[6,7]

Complementing the aforementioned 3-way activation system (Figure), it is worth understanding how each one acts. The classical pathway is triggered by antigen-antibody complexes and involves recognition by C1q and subsequent activation of C1r and C1s, culminating in the formation of C3 convertase (C4b2a).[6,23] The lectin pathway is initiated by the binding of mannose-binding lecithin (MBL) or phycolins to microbial surface carbohydrates. This complex activates serine proteases (MASP1 and MASP2) and cleaves C4 and C2, also resulting in C3 convertase.[7,23] The alternative pathway has a low-level spontaneous activation mechanism known as "tick over", where C3 is cleaved, binding to factor B. Cleavage by factor D originates C3 convertase (C3bBb).[7]

The three pathways converge to the cleavage of the C3 protein, followed by the action of C5 convertase over C5. This cleavage produces C5a, a highly inflammatory peptide, and C5b. The final step results in the formation of the membrane attack complex (MAC), which promotes osmotic lysis by inserting pores into the cell membrane.[5.23]



Source: Mariana D S Testa, 2025

FIGURE — Add-on system activation cascade

The pathophysiological role of C5a

C5a is the soluble fragment from the cleavage of C5. It is a potent pro-inflammatory peptide, acting through its G-protein-coupled receptors, which are chemoattractant and anaphylatoxin, cell activation, and cell adhesion and adaptive response.

In chemoattractant and anaphylatoxin, C5a recruits immune cells to the site of infection. It is classified as an anaphylatoxin due to its ability to act on mast cells and endothelial cells to promote a local inflammatory response that, in high concentrations, can lead to generalized circulatory collapse.

Cell activation promotes the activation of resident mast cells, leading to the release of inflammatory mediators, such as histamine and TNF-α.[7]

In cell adhesion and adaptive response, the action of

C5a contributes to the initiation of the adaptive immune response by recruiting phagocytic cells and accelerating the movement of antigen-presenting cells (APCs) to local lymph nodes.[7]

Complement system and obesity

The inflammatory process in obesity focuses on adipose tissue, where fat accumulation and adipocyte hypertrophy promote pathogenic changes. These alterations contribute to the increase of pro-inflammatory cytokines and, consequently, to the production and high serum levels of the C3 and C4 components of the complement system, which is associated with the induction of metabolic and cardiovascular diseases.[5,24] Activation of the complement system in obesity culminates in the cleavage of C5 into C5a. However, the precise involvement of the C5a–C5aR axis in the pathological mechanisms of obesity and insulin resistance, while crucial, still requires further investigation.[24]

Bariatric surgery and obesity control

Clinical treatment for obesity, based on lifestyle changes and pharmacological interventions, often encounters barriers in achieving lasting weight reduction goals.[5,25] Due to the low efficacy in weight maintenance with clinical treatment alone, bariatric surgery has been consolidated as the most effective intervention for severe obesity. It promotes significant and lasting weight loss, favoring the remission of associated diseases, increasing longevity and improving quality of life. Currently, surgical risks are considered low.[26] The new guidelines of the International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO)27 expanded the indications for patients with a BMI between 30-35 with uncontrolled T2DM. Among the techniques, gastric bypass with Roux-en-Y intestinal bypass is the most used in Brazil, providing a loss of 70-80% of excess weight and being highly effective in the remission of comorbidities.[28-31]

CONCLUSION

Serum levels of the pro-inflammatory anaphylotoxin C5a showed a significant and consistent reduction after the surgical intervention. Although there was a robust reduction in C5a associated with metabolic improvement, no statistically significant correlations were observed between C5a variation and anthropometric and cardiometabolic variables. In summary, bariatric surgery is effective in remission of comorbidities and in reducing the systemic inflammatory profile, supported by the significant drop in C5a levels.

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