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# Is the Immunogenic Action of Gluten Enough to Aggravate Obesity in Non-coeliac Individuals?

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**Abstract**

The pathogenesis of obesity involves a chronic low-grade inflammation. Gluten has been involved in rupture of intestinal barrier, disorganization of the intestinal junction complex and changes in intestinal microbiota. These actions favor the absorption of immunogenic components (such as LPS and several gliadin derivate peptides) to the submucosa and intensify the chronic low-grade inflammation seen in obesity.

In mice, gluten intake was associated to down regulation of proteins involved on browning process, reduction of thermogenesis and increase of pro-inflammatory cytokine expression in adipose tissue. Nevertheless, other studies showed that gluten-free diets were associated to nutrient unbalance, obesogenic microbiota profile and metabolic syndrome.

Despite the growing number of in vitro and experimental evidences suggesting that gluten could facilitate the development of obesity by inducing inflammation and altering energetic metabolism, no consensus has been established. Obesity is the result of a complex interaction of nutrients that act favoring or preventing the expansion of adipose tissue. Despite our knowledge about the immunogenic role of gluten, until controlled clinical studies confirm (or deny) the efficacy of GFD on weight loss, positions in favor or against gluten-free diet to treat or to prevent obesity are merely speculative.

**Keywords:** Gluten; Obesity; Inflammation; Gliadin; Zonulin; Microbiota

## Introduction

Obesity is an epidemic disease involved in the development of type 2 diabetes, hypertension and cardiovascular diseases, accompanied by chronic low-grade inflammation due to activation of immune cells in the expanded adipose tissue.

In a recent survey, about half of global responders described themselves as overweight, and about 50% of them are trying to lose weight [1]. Every day new diets and food strategies are published, claiming to prevent or reduce overweight and obesity. Gluten-free diet (GFD) has gained popularity for this finality, believing that this diet contributes to a better health and healthier eating. In the United States, market for gluten-free products has growed mainly due to non-celiac individuals who adhere GFD [2]. However, despite its popularity, association of gluten and obesity or weight loss is still inconsistent.

The pathogenesis of obesity involves changes in both innate and adaptive immune response, responsible for chronic low-grade inflammation, which in turn causes metabolic unbalance and chronic disease (e.g. type-2 diabetes, cardiovascular disease). Gut microbiota is now considered a key factor regulating events that can trigger the obesity-associated low-grade inflammation. Diet (especially high-fat diets) and others obesity-associated factors lead to changes in gut microbiota and intestinal permeability, contributing to this low-grade inflammation [3]. Both, diet and microbiota, up-regulate receptors of innate response in extra intestinal organs and trigger several signal pathways that lead to inflammatory cytokine release and inflammatory cell recruitment.

Microbiota dysbiosis is related to the release of zonulin, a protein that modulates junctional complex [4]. Zonulin is related to the increase of intestinal permeability, propitiating the access of intestinal antigens (such as LPS) to submucosa [5]. The presence of this antigens in the submucosa triggers the immune response related to the chronic low-grade inflammation seen in obesity [6]. In fact, high levels of blood zonulin were observed in individuals with obesity [7,8].

One of the dietary factors that has been linked to the disruption of intestinal barrier is the gluten. A crescent number of evidences has supported a deleterious effect of gliadin - the main protein of gluten -on intestinal permeability. Gliadin, is only partially digested by enzymes of gastrointestinal tract, resulting in the formation of peptides rich in glutamine and proline. Glutamine is the preferred substrate for deamination by intestinal transglutaminase (tTG). This enzyme may catalyze the crosslinking of gliadin, forming antigenic neoepitope [like gliadin-tTG complexes) that will initiate the immune response, especially (but not only) in genetically susceptible individuals [9]. In addition, the presence of proline determines a higher resistance to gastrointestinal proteolysis, which hampers an effective intestinal absorption [10]. Moreover, gliadin seems to have at least 50 epitopes with cytotoxic and immunomodulatory properties capable of influence intestinal permeability [11].

Gliadin or its peptides may access submucosa and extra-intestinal tissues due to increased intestinal permeability via zonulin signal [12]. Initially, gliadin (or its peptides) binds to the chemokine receptor CXCR3 that is crucial for the release of zonulin [13]. Zonulin binds its receptor in enterocytes and induces the polymerization of intracellular actin filaments that are directly connected to the junctional complex. It results in changes of cell morphology, such the reorganization of cytoskeleton, displacement of ZO-1 protein from the junctional complex, and disassembly of other tight junction proteins (occludin, claudin-1 and claudin-4) [4,12]. The weakness of intestinal barrier propitiates paracellular translocation of gliadin to the submucosa. There, gliadin triggers an immune response that induces interleukin (IL)-8 production and recruit neutrophils to this site [14]. In agreement with those findings, high levels of circulating gliadin-activated zonulin were described not only in CD patients, but also in non-CD individuals [7]. It suggests that gluten could impose changes on intestinal on microbiota composition and increase the intestinal permeability, facilitating the access of immunogenic components and contributing for exacerbation of chronic low-grade inflammation seen in obesity.

Nonetheless, gluten may also induce beneficial effects on immune response and on microbiota profile.

The consequences of GFD on energetic metabolism are poorly explored. Soares et al. [15] in a murine model of diet-induced obesity compared the effects of two isocaloric, isoproteic diets supplemented or not with 4.5% of gluten isolate. The Gluten-free group presented reduction in weight gain and adiposity, without changes in food intake, blood or fecal lipids. These results were associated with up-regulation of peroxisome proliferator-activated receptor PPAR alpha, gamma and enzymes related to lipid metabolism (lipoprotein lipase, hormone sensitive lipase and carnitine palmitoyl transferase-1). The Gluten-free diet also improved insulin sensibility, in agreement with the increased expression of adiponectin, insulin and GLUT4 as well as the reduction of resistin in adipose tissue. Moreover, intravital microscopy confirmed the proinflammatory role of gluten. Animals fed on gluten–free diet showed lower number inflammatory cell migrating to mesenteric tissue. In a similar study, Freire et al. [16] evaluated absorption and bio-distribution of orally administered (99m)Technetium radiolabeled with gluten. They demonstrated that gluten or its peptides reaches blood and tissue such adipose tissue, liver, spleen and lung. In adipose tissue, gluten-rich diet was associated to lower expression of UCP-1 and other proteins involved in the browning process, and to a reduction of thermogenesis. Increase of interleukin-6 expression were also seen in cultures of isolated adipocytes from obese mice receiving gluten [16].The results of Freire and colleagues are in agreement with clinical studies showing that gliadin residues reach serum and breast milk in a significant concentration of 41ng/mL [17,18].

Taking into consideration all these evidences about the immunogenic role of gluten, what could we conclude about the efficacy of GFD in obesity treatment? Since gluten is an incomplete protein, its exclusion unlikely will lead to a significant nutritional health risks in term of protein status. However, gluten-containing foods and preparations are also sources of fiber and polysaccharides. It has been described nutrient deficits (such as fiber, iron and complex B vitamins), increased intake of fat and potential toxicity (presence of arsenic and mercury) consequent to the intake of gluten-free products [19]. Concerns are also raised about risk of metabolic syndrome in those adhering GFD due to the high density of gluten-free foods that may affect leptin metabolism, inhibiting the bind between leptin and its receptor [20,21].

Gluten free diets are sometimes confounded with low-carb diets, because wheat is present in several popular food recipes. On the other hand, gluten exclusion may impose food restrictions that will lead to negative energetic balance and weight loss. However, studies comparing iso-energetic diets with and without gluten are rare in literature.

The belief that gluten free diets help to treat obesity did not emerge from controlled researches but rather, from personal impressions and reports published in books, without any proof of evidences. Thereafter, gluten became a villain and gluten-free diets, a synonym of healthy behavior. Ours and other groups have shown that gliadin or its peptides may trigger inflammatory responses and alter energetic metabolism. However, energy balance, the pillar of obesity development, is the result of a complex interaction of nutrients that act favoring or preventing the expansion of adipose tissue.

Other nutrients were also unequivocally related to changes in energetic metabolism without, however, influence clinical development of obesity. For instance, the saturated


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fatty acids which, like gluten, are able of increase the intestinal permeability, providing a low-grade inflammation state. However, low-fat diets, without a reduction in energy intake, do not result in weight loss. Nonetheless, high-fat diets, such as ketogenic ones, may induce a greater loss weight, regardless their content of fat [22]. At this point, clinical studies are necessary to evaluate the role of normal or excessive gluten intake on weight changes.

## Conclusion

In conclusion, despite our knowledge about the immunogenic role of gluten, until controlled clinical studies confirm (or deny) the efficacy of GFD on weight loss, positions in favor or against gluten-free diet to treat obesity are merely speculative.

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## Author Disclosures

we declare no economic interest or conflict of interest.

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