

Adverse Effects of Gluten-free Diets

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Abstract In celiac disease, treatment with a gluten-free diet is highly effective for management of clinical features, particularly resolution of diarrhea and weight loss. In children, normalization of growth results. In adult celiacs with iron deficiency anemia, complete normalization of iron levels and resolution of anemia may occur with a gluten-free diet alone. In addition, the small intestinal mucosa responds to restriction of dietary gluten and, eventually, in the vast majority, complete histological recovery occurs. Although effective in celiac disease, the gluten-free diet has been increasingly used in clinical conditions unrelated to celiac disease. Unfortunately, gluten-free diets may have significant negative effects with evidence for development of nutrient deficiencies, an increased risk for obesity particularly in children, and measurable evidence for the accumulation of several heavy metals in blood and urine. Although longer term studies are still needed, caution must be advised in the use of gluten-free diets for non-celiac disorders including those based solely on patient-reported gluten sensitivity

Keywords: *celiac disease, negative effects of gluten-free diets, heavy metals, fiber, gluten sensitivity*

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1. Introduction

Celiac disease is an immune-mediated enteropathy that leads to altered structure and function in the intestine [1]. Malabsorption, diarrhea, weight loss and other extra-intestinal manifestations may result. Although a number of disorders can cause similar structural and functional changes in the small intestine, only in celiac disease can a gluten-free diet lead to resolution and a return to normal of the clinical, serological and pathological features that led to the initial examination. The importance of a thorough evaluation of a patient suspected to have celiac disease including critical assessment after a gluten-free diet has been initiated to confirm diagnosis of this gluten-dependent disorder [2]. Overall, serological screening studies have suggested that up to 1 to 2 percent of populations may be affected by celiac disease, while biopsy screening of symptomatic referred patients result in higher yields [3].

2. Gluten Proteins

Gluten represents a heterogeneous group of proteins, mainly as gluten and gliadin, that serve the function of energy storage. They are derived from the starchy endosperm of cereal grains found in wheat, barley and rye. These are largely responsible for the viscoelastic properties of dough and bread products. Wheat and other grains improve the palatability of foods in the diet and enhance the production of foods with a high nutritional value. Indeed, it is believed that development of wheat

cultivation *per se* was the single most important factor that permitted survival advantage over hunter-gatherers in the Fertile Crescent about 10,000 years ago [4].

These prolamines proteins, once ingested, require processing in the human gastrointestinal tract. They are long peptides with high proline and glutamine content and, as a consequence, may be difficult to digest. They are complex molecules with many repetitive amino acid sequences and as many as 45 different gliadins may be derived from a single wheat variety. They may be further classified based on differing electrophoretic motility characteristics with each protein having different biological properties, particularly in relation to immune cell recognition and immune activation [5].

3. Non-Celiac Gluten-Sensitivity (NCGS)

In recent years, increased use of gluten-free products has occurred, not only due to increased detection of celiac disease *per se* (due to widespread serological screening as well as increased awareness by physicians and the general public for celiac disease), but also because of the emergence of so-called “gluten-related” diseases. A specific descriptive term, “*non-celiac gluten-sensitivity*” (NCGS), has been coined to suggest a possible, even intimate, relationship with celiac disease *per se*. Unfortunately, the evidence to support any direct relationship of this new “disease” to celiac disease is limited. Diagnosis of NCGS is largely related to patient-reported symptom improvement following removal of wheat or other grains, and specifically, dietary gluten, in some individuals. But, improvement is often transient and associated with the need to exclude an increasing number

of other dietary products (causing similar symptoms). The cause of symptoms is not readily explained in these individuals and clinical symptoms in NCGS often overlap with common symptoms of functional or dysfunctional gastrointestinal disorders, including the “irritable bowel syndrome”, or IBS. Finally, re-challenge studies with gluten-containing diets in those with NCGS have demonstrated that most do not develop recurrent symptoms [6,7]. And yet, ironically, individuals without convincing evidence of celiac disease may represent a significant global driving force for increased consumption of gluten-free diets. Of course, underlying all of this is the dramatic rise in marketing and sales of gluten-free products to the tune of more than 15 billion \$US in 2016, a substantial increase in the past quarter century [5]. To further justify the use of gluten-free diet, some have even claimed that dietary gluten may be harmful, and, by extension, that gluten restriction, rather than consumption, may be more in keeping with a healthy lifestyle [8].

Quite the opposite may be true. Studies examining the effects of gluten-free diets are limited. With the rising popularity of this “gluten-free life style” in individuals without celiac disease, added information has increasingly become available exploring the adverse or potential negative health effects of the gluten-free diet in otherwise healthy individuals as well as patients with celiac disease.

3.1. Nutrient Deficiency with Gluten-free Diets

In celiac disease, other disease related deficiencies or changes related to the underlying inflammatory process may be significant and could, in themselves, impact or confound the results and interpretation of studies thought to be focused solely on the gluten-free diet *per se*.

In a recent survey on adults with celiac disease related to the nutritional quality of a gluten-free diet, the recommended amounts of calcium, iron and fibre respectively were achieved for 31%, 44% and 46% of adult females and 63%, 100% and 88% of adult males [9]. Some gluten-free foods may also be limited in fiber, folic acid and other vitamins, such as niacin, riboflavin and thiamine [10,11]. Further longitudinal studies on gluten-free diet consumption in non-celiac patients known to have otherwise architecturally normal small intestinal mucosa would be useful to further define safety of gluten-free diets.

3.2. Nutrient Composition in Gluten-free Diets

Some studies have also explored the specific nutritional composition of processed gluten-free products [12,13]. In a study of adolescents with celiac disease compared to healthy age-matched controls, adherence to a strict gluten-free diet increased protein and lipid consumption [12]. In a study of celiac children compared to age- and sex-matched controls [13], significant reductions in anthropometric, biochemical and bone densitometric assessment were detected in celiacs. However, after a year on a gluten-free diet, no significant differences in measured parameters were defined in patients and controls,

except in height and arm muscle area. In contrast, serum hemoglobin, iron and zinc values below the normal range in half of patients at diagnosis were within the normal range for all after 1 year on a gluten-free diet. Serum hemoglobin, iron, zinc, triglycerides, proteins, albumin and calcium levels rose significantly during the year of gluten-free diet treatment. Some alterations may simply be “behavioral”, rather than related to the composition of gluten-free diets *per se*. In a recent report, results suggested that initiation of a gluten-free diet in children may lead to changes in eating habits and stable food eating in both children themselves as well as their families. As a result of a gluten-free diet, a more obesogenic environment may result [14]. As a result of the gluten-free diet, the families in this study apparently consumed more junk food, including snacks and candies, particularly in children and fathers. This has implications for children with celiac disease and their families consuming a gluten-free diet with respect to a healthier lifestyle and further long-term studies are needed.

3.3. Heavy Metal Accumulation with Gluten-free Diet

It is recognized that fish and rice, often a component of gluten-free diets, have high concentrations of some heavy metals, including arsenic, mercury, lead and cadmium. In part, this may reflect exposure of these food sources to heavy metal concentrations in water and agricultural soils. In a recent population survey, patients consuming gluten-free diets were evaluated for different heavy metals in blood and urine [15]. Results showed that total blood mercury, lead and cadmium levels were higher in those on a gluten-free diet. Urine levels of arsenic were also increased. These findings were particularly significant for those on a gluten-free diet, but without celiac disease. As noted elsewhere [16], the significance of these findings is not known. Higher exposure to heavy metals may result in higher cumulative exposure and higher bio-accumulation, but it is not known if a threshold can be reached with negative health consequences, particularly in those without celiac disease. The long-term effects of accumulation of these heavy metals in persons on a gluten-free diet deserve further study, particularly in those without celiac disease.

4. Gluten-free Diets in Treatment

While earlier surveys in patients diagnosed with celiac disease indicate that clinical features improved and recovery of symptoms [17,18], later studies have confirmed that histological improvement also occurs in the vast majority of patients with celiac disease treated with a gluten-free diet alone [19]. Indeed, even iron deficiency anemia in celiacs may be resolved simply with a gluten-free diet without the need for added oral iron supplementation [20]. In contrast, in those consuming a gluten-free diet for reasons other than proven celiac disease, measurable benefits may be difficult to document. Indeed, in those without celiac disease, a significant long-term health risk may result from use of gluten-free diets.

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