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Review Article

Gluten-Free Diets and Potential Adverse Effects

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Abstract

Celiac disease is a genetically-based life-long immune-mediated small intestinal mucosal disorder caused by gluten peptides found in wheat and other grains that may result in diarrhea, malabsorption and weight loss. A gluten-free diet usually leads to clinical improvement and resolution of abnormal small intestinal mucosal changes. In so-called "non-celiac gluten sensitivity", gluten-free diets appear to improve symptoms in some affects patients even though mucosal changes are not evident. Regardless, a strict gluten-free diet represents a significant lifestyle change for all using this diet due its significant inconvenience and financial burden. Although high gluten diets fail to cause mucosal injury, a strict life-long gluten-free diet may potentially result in unintended consequences including the effects of superimposed nutrient deficiencies, increased accumulation of some heavy metals and metabolic changes, including fatty liver and re-feeding syndromes. Physicians caring for patients on a gluten-free diet should be alert to potential adverse effects of their long-term use.

Keywords: Breast Tumor; Phyllodes Tumor; Prognostic Factors

Introduction

Celiac disease (gluten-sensitive enteropathy, celiac sprue) is a life-long immune-mediated small intestinal mucosal disorder that develops in genetically-predisposed persons. The disease leads to altered structure and function of the small intestine. The disorder is thought to be caused by gluten-peptides in wheat and other grains, usually leading to diarrhea, malabsorption, weight loss and other extra-intestinal changes. A strict gluten-free diet with removal of the offending peptide generally results in clinical improvement and resolution of mucosal changes [1-3]. Gluten-free diets may also be used by some with symptoms that are thought to be due to gluten but structural or functional changes are not detected (i.e., defined as so-called "non-celiac gluten sensitivity") [4]. In all, regardless of the clinical label or diagnosis, initiation and use of a gluten-free diet represents a substantial lifestyle and dietary change owing to the ubiquitous presence of gluten in many food products along with the increased inconvenience and financial cost to acquire specialized gluten-free dietary products [3]. However, detailed evaluations of gluten-free diets, especially if used over prolonged periods are limited. As a result, the increasingly popular "gluten-free lifestyle", especially in those without documented celiac disease, needs repeated dietary re-evaluation particularly for potentially negative health effects.

Beneficial effects of gluten-free diet in celiac disease

In celiac disease, a gluten-free diet usually leads to an improved clinical state within weeks of initiation along with improved nutrient absorption, weight gain, and improvements in small intestinal mucosal architecture. These occur well beyond changes that might be attributed to a simple placebo effect alone. Detailed studies [5] have demonstrated that the majority of those with severely abnormal biopsy changes improve histologically towards normal mucosa in repeated biopsies within 2 years of strict diet adherence, although in some, a more prolonged period may be required before improved changes can be documented [5]. Indeed, a much shorter period of less than 1 year in some patients may be sufficient to resolve mucosal biopsy changes and confirm the diagnosis of a gluten-sensitive disorder [5].

An improved immune status also results after gluten-free diet treatment in celiac disease as reflected in normalization of previously elevated measures of serum auto-antibodies, including IgA anti-tissue transglutaminase (or, tTG), the latter often used as a possible screening test for celiac disease before treatment. Although tTG values may improve after gluten-free diet treatment, this improvement may be clinically misleading, however, as the small intestinal mucosal inflammatory process may be ongoing and not fully resolved even though the tTG has normalized.

Studies of high gluten diets on the normal small bowel

In contrast, small intestinal mucosal changes induced by the addition of a gluten to the diet are reported not to occur in healthy volunteers, specifically in biopsy studies of the small intestine. In an important study published over 50 years ago in 1966 [6], a dose of gluten up to 150 grams per day was administered to healthy volunteers over 8 weeks in a hospital metabolic ward.

Changes in multiple small intestinal mucosal biopsies did not occur, observations further confirmed by an external expert histopathologist review. Similarly, no changes could be induced in 13 healthy siblings of children with celiac disease [7]. Similar gluten feeding studies in disorders closely linked to celiac disease, dermatitis herpetiformis [8] and lymphoma [9], demonstrated the development of a gluten-induced mucosal biopsy lesion that could be reversed back to normal with a gluten-free diet (i.e., so-called "latent celiac disease"). Interestingly, patients with lymphocytic colitis with normal small bowel biopsies were also evaluated in a similar fashion after a high gluten-diet, but evidence in these 2 specific patients for underlying and previously associated with celiac disease could not be documented as there were no induced biopsy changes [10].

Gluten is structurally and historically heterogeneous

Gluten is a heterogeneous group of proteins, that includes gliadin and these are thought to mainly serve as a vehicle for energy storage in different cereal grains. They are largely derived from the starchy endosperm of wheat, barley and rye, and possibly others. They appear to be responsible for the viscoelastic roles of dough and other bread products along with improved palatability of food and have resulted in enhanced production of various food products of high nutritional value.

Some think that wheat cultivation measures allowed survival advantage over hunter-gatherers approximately 10,000 to 12000 years ago in the region of the Fertile Crescent, particularly in eastern Turkey near the recently discovered archeological site, the Gobleki Tepe [11]. Here, the Einkorn wheat species is present growing on the slopes of a shield volcano with DNA fingerprinting studies confirming this to be the initial site of wheat domestication [12]. An early description of "The Coeliac Affection" was also attributed to Aretaeus in Cappadochia in Eastern Turkey during the second century AD was noted by Francis Adams in a lecture to the Sydenham society in 1856 [13]. An even earlier report of a young woman in Italy from the first century AD was also suspected to be an early case of celiac disease [14]. Later, studies by Dicke and his colleagues from the Netherlands in starving children during the second world war led to critical recognition of gluten as the likely offending agent [15].

Once consumed, these prolamine-containing proteins are hydrolyzed in the gastrointestinal tract. They are long peptides, rich in prolamine and glutamine, and are difficult to assimilate. As a result, complex molecules with many differing amino acid sequences result with up to 45 different gliadins derived from a single variety of wheat. Most present-day varieties of wheat have been genetically linked to the ancient Einkorn variety defined in the Cappadochia region of Eastern Turkey. Each gluten protein has been subsequently classified based on different electrophoretic mobility features and also have a range of biological properties, especially for immune cell recognition and immunological activation .

Gluten-free diets and nutrient deficiency

In general, malabsorption in celiac disease may lead to one or more specific nutrient deficiencies that could potentially confound results of studies believed to be focused solely on the gluten-free diet per se. However, in a recent study on nutritional quality of the gluten-free diet in treated adults with celiac disease, recommended amounts of calcium, iron and fibre were achieved for only 31%, 44% and 46% of adult females, respectively, and 63%, 100% and 88% of adult males, respectively [16]. Measures of folic acid, iron and fibre content in gluten-free diets have been described as limited while content of thiamin, riboflavin and niacin may be significantly reduced [17]. Further long-term studies of effects of gluten-free diet consumption on micronutrients in celiac disease would be useful. Similarly, longitudinal studies of non-celiac patients with normal small intestinal mucosa (i.e., specifically those with non-celiac gluten sensitivity") might also be important to ensure that gluten-free diets do not cause unintended nutrient deficiencies after prolonged use [18].

Interestingly, in adolescents with celiac disease on a strict gluten-free diet, increased protein and lipid consumption were defined compared to age-matched control participants [19]. In a further study of children with celiac disease compared to age- and sex-matched controls, reduced anthropometric, bone densitometric and biochemical results were noted in celiacs. But, after 1 year on a gluten-free diet, no differences were noted except for height and arm muscle area. However, hemoglobin, serum iron and serum zinc values were below normal for all participants after 1 year on a gluten-free diet. Also observed was a rise in hemoglobin, serum iron, zinc, triglycerides, proteins, albumin and calcium during the year on gluten-free diet treatment. Some of these changes suggest-

ed these reflect a "behavioral" affect rather than an affect of the gluten-free diet per se. The findings in children may have reflected altered eating habits for not only the children, but their entire families [20]. Families in this study also consumed more junk food, snacks and candies, especially in children and their fathers. Added studies are needed in the future focused on the effects of healthier lifestyles over the long term.

Heavy metal accumulation

Rice and fish are frequent components of gluten-free diets, and in some of these, especially high concentrations of arsenic, mercury, lead, cadmium and other heavy metals may be detected, possibly reflecting their exposure in soil and water prior to human consumption. Increased levels of total blood mercury, lead and cadmium were observed in those consuming gluten-free diets along with increased urine levels of arsenic [21], particularly in those without celiac disease [22]. Although noteworthy, the biological significance of these findings remains to be determined, especially in those without celiac disease treated with a gluten-free diet over the long term.

Importantly, in patients recently diagnosed with celiac disease and also determined to be iron deficient, supplemental iron alone may be ineffective in treating an associated anemia. The key element appears to be mucosal healing after institution of a gluten-free diet. Indeed, there is evidence that a gluten-free diet alone without supplements of iron is sufficient to manage the iron deficiency anemia [23].

Metabolic changes and fatty liver

Significant metabolic changes occur in celiac disease with gluten-free diet treatment, including a significant percentage with development of fatty liver [24-28]. Several reasons have been suggested for this development including improved nutrient absorption, greater intake of saturated fat to improve gluten-free diet palatability and a higher intake simple carbohydrates [24-28]. In some, it has been postulated that this may relate to altered bile acid signaling [29]. Others have suggested that proton pump inhibitors may be an added risk factor in celiac disease patients on a gluten-free diet [30]. Similar observations of the metabolic syndrome and fatty liver development have been reported even in asymptomatic celiacs defined only by a positive endomysial antibody test [31].

Re-feeding syndromes

An extension of these metabolic changes includes the re-feeding syndrome, most often recognized in hospital in-patient populations with anorexia within days of initiation of re-feeding (sometimes often during infusions of large nutrient loads with intravenous parenteral nutrition). Other changes may be noted in this setting including electrolyte disturbance, including hypokalemia. In ambulatory patients, this re-feeding syndrome may be more difficult to appreciate. Recently, a post-pubertal male with celiac disease recently started on a gluten-free diet increased his caloric intake with the appearance of a transient form of physiologic gynecomastia [32]. Although other causes of gynecomastia require exclusion in this setting, including medications, hepatic and renal disease and neoplastic disorders (e.g., testicular tutors), careful monitoring to exclude the referring syndrome and exclusion of these co-existing disorders is important.

Conclusion

Management of celiac disease patients needs to continue long after a diagnosis has been established and successful treatment with a gluten-free diet has been noted. Beneficial effects, not withstanding, there is the potential for other adverse effects of a lifelong gluten-free diet. Recognition is important, not only in patients in celiac disease, but in those using gluten-free diets for other purposes.

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