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MINIREVIEWS

Endocrine manifestations in celiac disease

Hugh James Freeman

Hugh James Freeman, Department of Medicine (Gastroenterology), University of British Columbia, Vancouver, BC V6T 1W5, Canada

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Correspondence to: Hugh James Freeman, MD, CM, FRCPC, FACP, Department of Medicine (Gastroenterology), University of British Columbia, 2211 Wesbrook Mall, Vancouver, BC V6T 1W5, Canada. hugfree@shaw.ca
Telephone: +1-604-8227216
Fax: +1-604-8227236

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Abstract

Celiac disease (CD) is an autoimmune small intestinal mucosal disorder that often presents with diarrhea, malabsorption and weight loss. Often, one or more associated endocrine disorders may be associated with CD. For this review, methods involved an extensive review of published English-language materials. In children and adolescents, prospective studies have demonstrated a significant relationship to insulin-dependent or type 1 diabetes, whereas in adults, autoimmune forms of thyroid disease, particularly hypothyroidism, may commonly co-exist. In some with CD, multiple glandular endocrinopathies may also occur and complicate the initial presentation of the intestinal disease. In others presenting with an apparent isolated endocrine disorder, serological screening for underlying subclinical CD may prove to be positive, particularly if type 1 diabetes, autoimmune thyroid or other autoimmune endocrine diseases, such as Addison's disease are first detected. A number of reports have also recorded hypoparathyroidism or hypopituitarism or ovarian failure in CD and these may be improved with a strict gluten-free diet.

Key words: Pituitary insufficiency; Ovarian infertility; Celiac disease; Gluten-sensitive enteropathy; Endocrine disorders; Thyroiditis; Hypothyroidism; Diabetes; Adrenal insufficiency

Core tip: Celiac disease (CD) is an immune-mediated intestinal disorder that may be closely linked to a number of extra-intestinal disorders, particularly endocrine diseases. These include thyroiditis, particularly in adults, and insulin-dependent diabetes mellitus, particularly in children and adolescents. Other endocrine disorders have also been recorded, including adrenal insufficiency and pituitary disease. Usually, only a single endocrine gland is involved in CD, but changes in multiple different glands has also been recorded. If an endocrine disorder is present, screening for CD, even without gastrointestinal symptoms, has been recommended. In established CD, regular follow-up and evaluation for the possible appearance of an occult endocrine disorder may also be appropriate.

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INTRODUCTION

Celiac disease (CD) is an immune-mediated small intestinal disorder that occurs in genetically susceptible people and is characterized by an intolerance to gluten-containing proteins found in wheat, rye and barley grains. Most often, symptomatic persons present with diarrhea, nutrient malabsorption and weight loss associated with a mucosal inflammatory process in the proximal small intestine. Mucosal architecture may be severely altered in the duodenum and, with increasing severity, may extend for variable distances into more distal jejunum and ileum. It may be that the severity of the individual inflammatory response, the timing of its appearance as well as the extent and localization within the small intestine are genetically-programmed[1].

In recent years, the disorder has become increasingly appreciated even without significant gastrointestinal symptoms, being documented in up to 2% of the serologically-studied populations, and perhaps, higher in referred patients using endoscopic screening biopsies[2]. The disorder is not only common, but has been increasingly recognized as a phenotypically heterogeneous disorder. Increased clinician awareness as well as widespread use of serological testing for case-finding have been important factors in the emergence of this disorder, not only in the scientific community, but also in popular press.

As a result, clinical features attributed to celiac disease or its complications have been noted in other extra-intestinal sites, including endocrine manifestations. Of these, two endocrine disorders are particularly prominent, thyroiditis, especially, but not exclusively, in adults, and insulin-dependent diabetes, particularly, but also not exclusively, in children. This manuscript aims to increase awareness of endocrine changes in CD, especially if there are few or no gastrointestinal symptoms, discuss screening opportunities and provide added insight related to a long and personal experience in CD diagnosis and management.

THYROID DISEASE

Early reports with CD

Autoimmune thyroid diseases were associated with CD in some initial descriptive studies for both children and adults[3,4]. Some early case reports also noted a link with hyperthyroidism[5-7] while others reported an association with hypothyroidism[8-10]. Interestingly, the simultaneous occurrence of adult CD and lymphocytic thyroiditis was also noted and hypothesized to be more than coincidential[11]. In a later report[12] from a defined area in Scotland, studies for thyroid autoantibodies and measurements of thyroid function suggested that the risk of even clinically overt thyroid disease, especially hypothyroidism, was increased in CD. Some suggested that this may be genetically determined owing to the common detection of human lymphocyte antigen (HLA) haplotypes in most with autoimmune thyroid disease and CD compared to the general population[13-16].

Later prevalence studies in CD

An evaluation of 96 consecutive adults (70 females and 26 males) with biopsy-defined CD (*i.e.,* severe lesion, Marsh 3, crypt hyperplastic villous atrophy, followed by a clinical and biopsy-defined response to a gluten-free diet, average age diagnosis of CD, 47.3 years) revealed 16 with autoimmune thyroid disease (including 11 females and 5 males, overall average age of CD in this group with thyroid disease, 57.1 years). Of these, 16 had hypothyroidism, but 4 had previously received radio-iodine ablation or thyroidectomy for Grave's (hyperthyroidism) disease. Interestingly, almost half also had dermatitis herpetiformis, an autoimmune dermatological disorder closely linked to adult CD. None had familial CD or a familial thyroid disorder. Diagnosis of thyroid disease preceded diagnosis of CD in 13 patients or was made concurrently in 2 patients. Only 1 had thyroid disease detected about a decade after CD was first diagnosed and treated with a gluten-free diet. Of note, 4 also developed a small intestinal lymphoma or adenocarcinoma, both known complicating malignant disorders in adult CD.

These findings are similar to a more recent and larger prospective evaluation of 242 celiacs[17]. In this study hypothyroidism was present at a similar rate of 12.9%, 3-fold higher than controls of 4.2%. Most interesting were the results in those treated with a strict gluten-free diet for at least 1 year. In these, there was an apparent normalization of subclinical hypothyroidism. In 5 of 91 celiacs with normal thyroid function development of thyroid disease occurred. Others have noted autoimmune thyroid disease in 13.9% of 79[18] and 30.5% of 36 adult celiacs[19], respectively, similar in prevalence to earlier studies.

Pathogenetic linkages with CD

This linkage between adult CD and autoimmune thyroid disease is not entirely novel, particularly as HLA (human leukocyte antigen) haplotypes B8 and DR3 were noted to occur with increased frequencies in adults and children with CD as well autoimmune thyroid disease. Interestingly, HLA DR antigen was also demonstrated in other epithelial glandular structures in children and adults with autoimmune disorders (*e.g.,* salivary glands in Sjogren's syndrome)[20,21]. An alternate, but not necessarily entirely exclusive hypothesis is also possible. The thyroid gland shares a common embryonic origin during fetal development,

being derived from the pharyngeal gut on the 17th day. Some autoimmune disorders may also require time to evolve, perhaps increased intestinal permeability may allow excessive amounts of antigen to enter the circulation and cross-react with other tissues, including the thyroid gland.

Clinical implications

The linkage between these two disorders may have important clinical implications. A relatively high prevalence of autoimmune thyroid disease, particularly hypothyroidism, in elderly adults may make clinical recognition of CD, at times, difficult. For example, the severity of the diarrhea or weight loss may be more limited with reductions of circulating thyroid hormone leading to increased time for intestinal transit or fluid retention with myxedema. In addition, some with an altered bowel habit may have impaired absorption, particularly with an increased transit rate in hyperthyroidism. As a result, an apparent failure to respond to a gluten-free diet may be considered. In contrast, hypothyroid patients may fail to respond to oral thyroid replacement therapy because of reduced small intestinal surface absorptive area associated with unrecognized or occult CD.

Serological CD screening in thyroid disease

A number of recent studies have explored the role of serological screening for celiac disease in patients with autoimmune thyroid disease. In a study from Finland of 83 patients[22], 3 asymptomatic cases and 1 previously diagnosed celiac patient were defined for an overall frequency of 4.8%. In an Italian study of 152 patients, 5 new cases were detected using endomysial antibodies and duodenal biopsy confirmation[23]. Similar results were reported later by other investigators in both children and adults with CD[24-29]. Far less information is available in Grave's hyperthyroidism. In 115 consecutive patients with Grave's hyperthyroidism[30], gliadin and tissue transglutaminase antibodies were used to screen for CD. 5 patients were detected, although 2 were already known to have CD. All 5 (*i.e.,* 4.5%) were free of symptoms. On the basis of these studies, these investigators have suggested that patients with hypothyroidism or hyperthyroidism should have serological screening for CD.

Other thyroid disorder in CD

Finally, other thyroid disorders have been recorded in CD. Most intriguing are reports of malignant thyroid lymphomas with CD, given the increased risk of lymphoma, particularly T-cell enteropathy, in CD. In an early retrospective evaluation of 12 cases of malignant thyroid lymphoma, 2 had intra-abdominal lymphoma and 1 had documented adult CD[31]. In a later report, a thyroid mass from a lymphoma was described in adult CD[32]. In this instance, the lymphoma was noted to be a rare T-cell lymphoma, indicating another site of extranodal lymphoma that may complicate the clinical course of CD, possibly due to its shared embryological developmental links with the gastrointestinal tract.

DIABETES

Early reports in CD

A number of early reports first described the association between CD and diabetes mellitus, sometimes co-existing with thyroid disease[6,33]. Although most were noted in pediatric-aged patients, some older clinical series also described adults with this association[34-36].

Recent prevalence and screening studies

In recent years, a number of studies from North America[37,38] and Europe[39] reported an increased prevalence of type 1 diabetes in CD thought to be due to an autoimmune process targeting the insulin-producing islet cells of the pancreas[40]. In our investigations, 233 children and adolescents with type 1 diabetes were prospectively screened with serological markers for CD[41]. Sera were blinded and IgA endomysial (EMA) as well as IgA tissue transglutaminase (tTG) assays were done. Among these, 19 were positive for EMA and also had elevated tTG levels. Of these, 1 was already known to have CD while 18 others had minimal or no symptoms and small intestinal biopsies performed. Of these, 14 had moderate to severe morphological changes consistent with CD (along with 1 having normal biopsies and 3 with epithelial lymphocytosis), yielding an overall biopsy-confirmed prevalence of CD of 7.7%, a rate later confirmed by reports from different countries[42-47]. A recent meta-analysis pursued these observations further by urging screening for CD in type 1 diabetes, particularly in children[48].

Pathogenetic linkages

CD and type 1 diabetes mellitus are complex disorders with shared genetic components. The major histocompatibility complex (MHC) is known to be involved in the presentation of peptide antigen from gluten-containing foods to T-cells. MHC class Ⅱ DQ peptides may be associated with both celiac disease and type 1 diabetes. Specific genetic determinants, HLA-DQ2, *i.e.,* haplotypes (DR3-DQ2), occur in about 90% or more of patients with CD and over 50% with type 1 diabetes, while HLA-DQ8 has been reported to occur in about 10% of patients with CD and about 70% of type 1 diabetes[49]. There are several HLA and non-HLA loci in type 1 diabetes mellitus shared in CD[50,51]. Non-HLA genes, such as CTLA4, have also been noted in both CD and type 1 diabetes. For several of these, multiple genes are present[52]. In addition, other non-genetic or environmental factors likely play a role in pathogenesis of these autoimmune disorders[53].

Most intriguing are recent observations related to the intestinal luminal organisms. Often, viruses such

as enteroviruses and rotavirus have been noted[53-58]. Changes in the luminal environment have been hypothesized to alter the intestinal immune system, its regulation or intestinal permeability. The intestinal microbiome may also play a critical environmental role in genetically-predisposed individuals. An altered composition of the gut microflora has been reported in CD, including a decreased ratio of *Firmicutes* and *Bacteroidetes*[59,60]. As reviewed elsewhere, alterations in the intestinal microbiota have also been documented with dietary removal of gluten[61].

Although the precise mechanism for a possible pathogenic effect of gluten in type 1 diabetes is not known, the effects of a gluten-free diet on control of insulin-dependent diabetes mellitus have been explored. Most reported investigations involve studies with animal models. However, in a case report, remission was achieved in a male child with insulin-dependent diabetes without insulin therapy on a gluten-free diet alone[62].

Clinical implications

Time course studies of diagnosis of type 1 diabetes and CD suggests that diagnosis of type 1 diabetes usually occurs first, followed by CD[63-66]. In patients with type 1 diabetes and celiac disease, additional autoimmune diseases may later develop, particularly autoimmune thyroid disease[67-69]. Moreover, risk of disease complications, including bone disease, retinopathy or nephropathy may occur, particularly if concomitant CD is present[67-71], and symptoms associated with CD may be more difficult to resolve if type 1 diabetes is also present[69]. Finally, a gluten-free diet (if CD is present) may lead to better glycemic control and protect patients against development of diabetes-related vascular complications[70]. Clearly, further studies are needed to determine the impact of a gluten-free diet in patients with both diagnoses. In addition, added studies in pediatric and adolescent patients with both diagnoses may be important because of concerns related to compliance, especially in those with limited symptoms[71].

OTHER ENDOCRINE DISORDERS

Early and recent prevalence reports

Adrenal insufficiency and CD may occur in some patients. Indeed, a high frequency of adult CD may be present in association with autoimmune adrenocortical failure (autoimmune Addison's disease). Many occur in the setting of polyendocrine failure that may include Addison's disease, thyroiditis, ovarian failure and CD[72]. In a study of 76 patients (44 females) with Addison's disease from Norway, 5 had biopsy-confirmed changes of CD and 1 additional patient had a previous diagnosis of CD[73]. All had HLA haplotype DR3-DQ2 with a total prevalence of CD of 7.9%. Although 52% had evidence of polyglandular endocrine failure, the investigators recommended that Addison patients be screened for CD and suggested that causes of failure of substitute hormonal treatment may include CD. In a separate Swedish national registry study[74], both children and adults with CD had a significant positive association with Addison's disease. As there was no apparent temporal sequence in diagnosis of either disorder, it was recommended that cases with adrenal insufficiency be screened for CD, and that CD patients have increased awareness of adrenal insufficiency.

Autoimmune polyglandular syndromes

More recent reports have emphasized the significance of recognition of autoimmune polyglandular syndrome[75] in different age groups permitting definition of 2 major subtypes. A juvenile form (APS, type I) usually develops in early adolescence or infancy and appears to be characterized by multiple endocrine deficiencies, mucocutaneous candidiasis, ectodermal dystrophy and different endocrine disorders, including hypoparathyroidism and usually Addison's disease, type 1 diabetes, hypogonadism and thyroid disease. Another form usually occurs later in the 3rd or 4th decade (APS, type Ⅱ), with a female predominance. Endocrine diseases that occur commonly include autoimmune thyroid disease, type 1 diabetes and Addison's disease while hypoparathyroidism is rare and no mucocutaneous candidiasis develops[76]. Although hypoparathyroidism has been rarely recorded with coincident CD[77], the endocrine pattern in adult CD most often fits the type Ⅱ pattern[76]. In a very recent report, however, it was noted that in those with concurrent celiac disease and hypoparathyroidism, a gluten-free diet had a beneficial effect on calcium regulation[78].

In another report, the evolving nature of these autoimmune polyendocrine syndromes with CD was further emphasized[79]. The authors confirmed that APS Ⅰ most often developed in childhood and included hypoparathyroidism, mucocutaneous candidiasis and Addison's disease. The more common APS Ⅱ type was often diagnosed if Addison's disease occurred together with thyroiditis (Schmidt's syndrome) or type 1 diabetes (Carpenter's syndrome). Another form, APS 3, may be seen if there is no adrenal cortical defect. A further type 4 may occur if other less common autoimmune endocrine failure develops, specifically autoimmune hypophysitis, with CD[79]. The authors noted that the detection of a monoglandular endocrinopathy may only be part of an evolving and dynamic process with the appearance of other endocrinopathies at a later stage in CD. In contrast, an Italian study of children and adolescents noted a high detection rate (42%) of anti-pituitary antibodies in newly diagnosed celiacs[80]. Interestingly, high antibody levels were associated with height impairment, possibly mediated by a reduction in insulin-like growth factor, and suggesting that an autoimmune pituitary process may be important

in the induction of linear growth impairment in CD. Further mechanisms may be at play in growth failure in CD. A gluten-free diet has been reported to result in rapid catch-up growth and normalization of pituitary function[81] and some have suggested a possible role for growth hormone replacement in children with short stature, despite a gluten-free diet over a 1 year period[82]. Other evidence has accumulated that the pituitary gland may be altered in CD. For example, prolactin is produced by the anterior pituitary gland, may be important in breast glandular development and may play a role in autoimmune regulatory mechanisms. In some studies, prolactin levels were increased in recently diagnosed CD in pediatric patients and these levels decreased over a few months with a gluten-free diet[83,84].

Ovarian failure causing infertility is also becoming increasingly recognized in adult CD and has recently been reviewed[85]. Indeed, in some prospective serologically-based studies, over 4% of infertile females may prove to have CD. If positive, subsequent biopsy studies have confirmed the presence of adult celiac disease. In some of these, treatment with a gluten-free was associated with later subsequent successful pregnancy. A recent meta-analysis of relevant studies indicated that CD was more prevalent in women with "all-cause" and "unexplained" infertility compared to the general population[86].

CONCLUSION

In CD, a number of autoimmune endocrine disorders may occur. Often, these clinically present with monoglandular involvement, usually the thyroid gland in adults or with insulin-dependent (type 1) diabetes in children and adolescents as well as adults[87]. Similar observations have also recently been reported from China[88]. Polyglandular disease has also become increasingly recognized, sometimes in association with a long clinical course of undiagnosed CD prior to detection and institution of a gluten-free diet. Diagnosis of CD may eventually also lead to definition of a single or multiple gland autoimmune syndrome that may only result after repeated evaluations of the patient with CD.

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