**Name of journal:** ***World Journal of*** ***Gastroenterology***

**ESPS Manuscript NO: 28350**

**Manuscript Type: MINIREVIEWS**

**Endocrine manifestations in celiac disease**

Freeman HJ *et al.* Celiac associated endocrine disease

Hugh James Freeman

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

**Author contributions:** Freeman HJ is responsible for all of this manuscript.

**Conflict-of-interest statement:** There is no conflict of interest for the author in this manuscript.

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

**Manuscript source:** Invited manuscript

**Correspondence to: Dr. Hugh 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

**Received:** June 29, 2016

**Peer-review started:** June 30, 2016

**First decision:** July 29, 2016

**Revised:** August 5, 2016

**Accepted:** August 23, 2016

**Article in press:**

**Published online:**

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

**© The Author(s) 2016.** Published by Baishideng Publishing Group Inc. All rights reserved.

**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.

Freeman HJ. Endocrine manifestations in celiac disease. *World J Gastroenterol* 2016; In press

**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-programed[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[56].

 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.

**REFERENCES**

1 **Freeman HJ**, Chopra A, Clandinin MT, Thomson AB. Recent advances in celiac disease. *World J Gastroenterol* 2011; **17**: 2259-2272 [PMID: 21633592 DOI: 10.3748/wjg.v7.i18.2259]

2 **Freeman HJ**. Detection of adult celiac disease with duodenal screening biopsies over a 30-year period. *Can J Gastroenterol* 2013; **27**: 405-408 [PMID: 23862172 DOI: 10.1155/2013/347902]

3 **Cooper BT**, Holmes GK, Cooke WT. Coeliac disease and immunological disorders. *Br Med J* 1978; **1**: 537-539 [PMID: 630212 DOI: 10.1136/bmj.1.6112.537]

4 **Midhagen G**, Järnerot G, Kraaz W. Adult coeliac disease within a defined geographic area in Sweden. A study of prevalence and associated diseases. *Scand J Gastroenterol* 1988; **23**: 1000-1004 [PMID: 3201123 DOI: 10.3109/00365528809090160]

5 **Wall AJ**, Levinson JD, Refetoff S. Hyperthyroidism and adult celiac disease. *Am J Gastroenterol* 1973; **60**: 387-393 [PMID: 4758296]

6 **Chambers TL**. Coexistent coeliac disease, diabetes mellitus, and hyperthyroidism. *Arch Dis Child* 1975; **50**: 162-164 [PMID: 1130822 DOI: 10.1136/adc.50.2.162]

7 **Green PA**, Wollaeger EE. The clinical behavior of sprue in the United States. *Gastroenterology* 1960; **38**: 399-418 [PMID: 13851526]

8 **Kelley ML**, Stewart JM. Myxedema and intestinal malabsorption (nontropical sprue?) with severe hypomotility of the gastrointestinal tract: report of a case. *Am J Dig Dis* 1964; **9**: 79-86 [PMID: 14102691 DOI: 10.1007/BF02232684]

9 **Siurala M**, Varis K, Lamberg BA. Intestinal absorption and autoimmunity in endocrine disorders. *Acta Med Scand* 1968; **184**: 53-64 [PMID: 5755424 DOI: 10.1111/j.0954-6820.1968.tb02422.x]

10 **Robinson TJ**. Coeliac disease and goitre. *Postgrad Med J* 1977; **53**: 95-96 [PMID: 577610 DOI: 10.1136/pgmj.53.616.95]

11 **Kuitunen P**, Mäenpää J, Krohn K, Visakorpi JK. Gastrointestinal findings in autoimmune thyroiditis and non-goitrous juvenile hypothyroidism in children. *Scand J Gastroenterol* 1971; **6**: 336-341 [PMID: 5109236 DOI: 10.3109/00365527109181130]

12 **Troutman ME**, Efrusy ME, Bennett GD, Kniaz JL, Dobbins WO. Simultaneous occurrence of adult celiac disease and lymphocytic thyroiditis. *J Clin Gastroenterol* 1981; **3**: 281-285 [PMID: 7288122 DOI: 10.1097/00004836-198109000-00013]

13 **Counsell CE**, Taha A, Ruddell WS. Coeliac disease and autoimmune thyroid disease. *Gut* 1994; **35**: 844-846 [PMID: 8020817 DOI: 10.1136/gut.35.6.844]

14 **Stokes PL**, Asquith P, Holmes GK, Mackintosh P, Cooke WT. Histocompatibility antigens associated with adult coeliac disease. *Lancet* 1972; **2**: 162-164 [PMID: 4114064 DOI: 10.1016/S0140-6736(72)91330-X]

15 **Ek J**, Albrechtsen D, Solheim BG, Thorsby E. Strong association between the HLA-Dw3-related B cell alloantigen -DRw3 and coeliac disease. *Scand J Gastroenterol* 1978; **13**: 229-233 [PMID: 76332 DOI: 10.3109/00365527809181753]

16 **Farid NR**, Bear JC. The human major histocompatibility complex and endocrine disease. *Endocr Rev* 1981; **2**: 50-86 [PMID: 7028471 DOI: 10.1210/edrv-2-1-50]

17 **Sategna-Guidetti C**, Volta U, Ciacci C, Usai P, Carlino A, De Franceschi L, Camera A, Pelli A, Brossa C. Prevalence of thyroid disorders in untreated adult celiac disease patients and effect of gluten withdrawal: an Italian multicenter study. *Am J Gastroenterol* 2001; **96**: 751-757 [PMID: 11280546 DOI: 10.1111/j.1572-0241.2001.03617.x]

18 **Hakanen M**, Luotola K, Salmi J, Laippala P, Kaukinen K, Collin P. Clinical and subclinical autoimmune thyroid disease in adult celiac disease. *Dig Dis Sci* 2001; **46**: 2631-2635 [PMID: 11768252 DOI: 10.1023/A: 1012754824553]

19 **Carta MG**, Hardoy MC, Boi MF, Mariotti S, Carpiniello B, Usai P. Association between panic disorder, major depressive disorder and celiac disease: a possible role of thyroid autoimmunity. *J Psychosom Res* 2002; **53**: 789-793 [PMID: 12217453 DOI: 10.1016/S0022-3999(02)00328-8]

20 **Fox RI**, Bumol T, Fantozzi R, Bone R, Schreiber R. Expression of histocompatibility antigen HLA-DR by salivary gland epithelial cells in Sjögren's syndrome. *Arthritis Rheum* 1986; **29**: 1105-1111 [PMID: 3092835 DOI: 10.1002/art.1780290908]

21 **Arnaud-Battandier F**, Cerf-Bensussan N, Amsellem R, Schmitz J. Increased HLA-DR expression by enterocytes in children with celiac disease. *Gastroenterology* 1986; **91**: 1206-1212 [PMID: 3758613]

22 **Collin P**, Salmi J, Hällström O, Reunala T, Pasternack A. Autoimmune thyroid disorders and coeliac disease. *Eur J Endocrinol* 1994; **130**: 137-140 [PMID: 8130887 DOI: 10.1530/eje.0.1300137]

23 **Sategna-Guidetti C**, Bruno M, Mazza E, Carlino A, Predebon S, Tagliabue M, Brossa C. Autoimmune thyroid diseases and coeliac disease. *Eur J Gastroenterol Hepatol* 1998; **10**: 927-931 [PMID: 9872614 DOI: 10.1097/00042737-199811000-00005]

24 **Valentino R**, Savastano S, Tommaselli AP, Dorato M, Scarpitta MT, Gigante M, Micillo M, Paparo F, Petrone E, Lombardi G, Troncone R. Prevalence of coeliac disease in patients with thyroid autoimmunity. *Horm Res* 1999; **51**: 124-127 [PMID: 10461017 DOI: 10.1159/000023344]

25 **Cuoco L**, Certo M, Jorizzo RA, De Vitis I, Tursi A, Papa A, De Marinis L, Fedeli P, Fedeli G, Gasbarrini G. Prevalence and early diagnosis of coeliac disease in autoimmune thyroid disorders. *Ital J Gastroenterol Hepatol* 1999; **31**: 283-287 [PMID: 10425571]

26 **Berti I**, Trevisiol C, Tommasini A, Città A, Neri E, Geatti O, Giammarini A, Ventura A, Not T. Usefulness of screening program for celiac disease in autoimmune thyroiditis. *Dig Dis Sci* 2000; **45**: 403-406 [PMID: 10711459 DOI: 10.1023/A: 1005441400107]

27 **Volta U**, Ravaglia G, Granito A, Forti P, Maioli F, Petrolini N, Zoli M, Bianchi FB. Coeliac disease in patients with autoimmune thyroiditis. *Digestion* 2001; **64**: 61-65 [PMID: 11549838 DOI: 10.1159/000048840]

28 **Larizza D**, Calcaterra V, De Giacomo C, De Silvestri A, Asti M, Badulli C, Autelli M, Coslovich E, Martinetti M. Celiac disease in children with autoimmune thyroid disease. *J Pediatr* 2001; **139**: 738-740 [PMID: 11713456 DOI: 10.1067/mpd.2001.118189]

29 **Meloni GF**, Tomasi PA, Bertoncelli A, Fanciulli G, Delitala G, Meloni T. Prevalence of silent celiac disease in patients with autoimmune thyroiditis from Northern Sardinia. *J Endocrinol Invest* 2001; **24**: 298-302 [PMID: 11407647 DOI: 10.1007/BF03343864]

30 **Ch'ng CL**, Biswas M, Benton A, Jones MK, Kingham JG. Prospective screening for coeliac disease in patients with Graves' hyperthyroidism using anti-gliadin and tissue transglutaminase antibodies. *Clin Endocrinol* (Oxf) 2005; **62**: 303-306 [PMID: 15730411 DOI: 10.1111/j.1365-2265.2005.02214.x]

31 **Grimley RP**, Oates GD. The natural history of malignant thyroid lymphomas. *Br J Surg* 1980; **67**: 475-477 [PMID: 7417748 DOI: 10.1002/bjs.1800670708]

32 **Freeman HJ**. T cell lymphoma of the thyroid gland in celiac disease. *Can J Gastroenterol* 2000; **14**: 635-636 [PMID: 10978950 DOI: 10.1155/2000/582364]

33 **Walker-Smith JA**. Diabetes and coeliac disease. *Lancet* 1969; **2**: 1366 [PMID: 4188128 DOI: 10.1016/S0140-6736(69)90363-8]

34 **Walsh CH**, Cooper BT, Wright AD, Malins JM, Cooke WT. Diabetes mellitus and coeliac disease: a clinical study. *Q J Med* 1978; **47**: 89-100 [PMID: 674552]

35 **Shanahan F**, McKenna R, McCarthy CF, Drury MI. Coeliac disease and diabetes mellitus: a study of 24 patients with HLA typing. *Q J Med* 1982; **51**: 329-335 [PMID: 6755530]

36 **Collin P**, Salmi J, Hällström O, Oksa H, Oksala H, Mäki M, Reunala T. High frequency of coeliac disease in adult patients with type-I diabetes. *Scand J Gastroenterol* 1989; **24**: 81-84 [PMID: 2784589 DOI: 10.3109/00365528909092243]

37 **Fraser-Reynolds KA**, Butzner JD, Stephure DK, Trussell RA, Scott RB. Use of immunoglobulin A-antiendomysial antibody to screen for celiac disease in North American children with type 1 diabetes. *Diabetes Care* 1998; **21**: 1985-1989 [PMID: 9802755 DOI: 10.2337/diacare.21.11.1985]

38 **Hill I**, Fasano A, Schwartz R, Counts D, Glock M, Horvath K. The prevalence of celiac disease in at-risk groups of children in the United States. *J Pediatr* 2000; **136**: 86-90 [PMID: 10636980 DOI: 10.1016/S0022-3476(00)90055-6]

39 **Mäki M**, Huupponen T, Holm K, Hällström O. Seroconversion of reticulin autoantibodies predicts coeliac disease in insulin dependent diabetes mellitus. *Gut* 1995; **36**: 239-242 [PMID: 7883223 DOI: 10.1136/gut.36.2.239]

40 **Freeman HJ**. Pancreatic endocrine and exocrine changes in celiac disease. *World J Gastroenterol* 2007; **13**: 6344-6346 [PMID: 18081222 DOI: 10.3748/wjg.v13.i47.6344]

41 **Gillett PM**, Gillett HR, Israel DM, Metzger DL, Stewart L, Chanoine JP, Freeman HJ. High prevalence of celiac disease in patients with type 1 diabetes detected by antibodies to endomysium and tissue transglutaminase. *Can J Gastroenterol* 2001; **15**: 297-301 [PMID: 11381296 DOI: 10.1155/2001/640796]

42 **Mahmud FH**, Murray JA, Kudva YC, Zinsmeister AR, Dierkhising RA, Lahr BD, Dyck PJ, Kyle RA, El-Youssef M, Burgart LJ, Van Dyke CT, Brogan DL, Melton LJ. Celiac disease in type 1 diabetes mellitus in a North American community: prevalence, serologic screening, and clinical features. *Mayo Clin Proc* 2005; **80**: 1429-1434 [PMID: 16295022 DOI: 10.4065/80.11.1429]

43 **Hanukoglu A**, Mizrachi A, Dalal I, Admoni O, Rakover Y, Bistritzer Z, Levine A, Somekh E, Lehmann D, Tuval M, Boaz M, Golander A. Extrapancreatic autoimmune manifestations in type 1 diabetes patients and their first-degree relatives: a multicenter study. *Diabetes Care* 2003; **26**: 1235-1240 [PMID: 12663603 DOI: 10.2337/diacare.26.4.1235]

44 **Salardi S**, Volta U, Zucchini S, Fiorini E, Maltoni G, Vaira B, Cicognani A. Prevalence of celiac disease in children with type 1 diabetes mellitus increased in the mid-1990 s: an 18-year longitudinal study based on anti-endomysial antibodies. *J Pediatr Gastroenterol Nutr* 2008; **46**: 612-614 [PMID: 18493223 DOI: 10.1097/MPG.0b013e31815d697e]

45 **Djurić Z**, Stamenković H, Stanković T, Milićević R, Branković L, Cirić V, Katić V. Celiac disease prevalence in children and adolescents with type 1 diabetes from Serbia. *Pediatr Int* 2010; **52**: 579-583 [PMID: 20113423 DOI: 10.1111/j.1442-200X.2010.03085.x]

46 **Bhadada SK**, Kochhar R, Bhansali A, Dutta U, Kumar PR, Poornachandra KS, Vaiphei K, Nain CK, Singh K. Prevalence and clinical profile of celiac disease in type 1 diabetes mellitus in north India. *J Gastroenterol Hepatol* 2011; **26**: 378-381 [PMID: 21261730 DOI: 10.1111/j.1440-1746.2010.06508.x]

47 **Sari S**, Yeşilkaya E, Eğritaş O, Bideci A, Cinaz P, Dalgiç B. Prevalence of Celiac disease in Turkish children with type 1 diabetes mellitus and their non-diabetic first-degree relatives. *Turk J Gastroenterol* 2010; **21**: 34-38 [PMID: 20533110 DOI: 10.4318/tjg.2010.0045]

48 **Elfström P**, Sundström J, Ludvigsson JF. Systematic review with meta-analysis: associations between coeliac disease and type 1 diabetes. *Aliment Pharmacol Ther* 2014; **40**: 1123-1132 [PMID: 25270960 DOI: 10.1111/apt.12973]

49 **Hermann R**, Turpeinen H, Laine AP, Veijola R, Knip M, Simell O, Sipilä I, Akerblom HK, Ilonen J. HLA DR-DQ-encoded genetic determinants of childhood-onset type 1 diabetes in Finland: an analysis of 622 nuclear families. *Tissue Antigens* 2003; **62**: 162-169 [PMID: 12889996 DOI: 10.1034/j.1399-0039.2003.00071.x]

50 **Kumar V**, Wijmenga C, Withoff S. From genome-wide association studies to disease mechanisms: celiac disease as a model for autoimmune diseases. *Semin Immunopathol* 2012; **34**: 567-580 [PMID: 22580835 DOI: 10.107/s00281-012-0312-1]

51 **Smyth DJ**, Plagnol V, Walker NM, Cooper JD, Downes K, Yang JH, Howson JM, Stevens H, McManus R, Wijmenga C, Heap GA, Dubois PC, Clayton DG, Hunt KA, van Heel DA, Todd JA. Shared and distinct genetic variants in type 1 diabetes and celiac disease. *N Engl J Med* 2008; **359**: 2767-2777 [PMID: 19073967 DOI: 10.1056/NEJMoa0807917]

52 **Cohn A**, Sofia AM, Kupfer SS. Type 1 diabetes and celiac disease: clinical overlap and new insights into disease pathogenesis. *Curr Diab Rep* 2014; **14**: 517 [PMID: 24952108 DOI: 10.1007/s11892-014-0517-x]

53 **Sadeharju K**, Hämäläinen AM, Knip M, Lönnrot M, Koskela P, Virtanen SM, Ilonen J, Akerblom HK, Hyöty H. Enterovirus infections as a risk factor for type I diabetes: virus analyses in a dietary intervention trial. *Clin Exp Immunol* 2003; **132**: 271-277 [PMID: 12699416 DOI: 10.1046/j.1365-2249.2003.02147.x]

54 **Lönnrot M**, Knip M, Roivainen M, Koskela P, Akerblom HK, Hyöty H. Onset of type 1 diabetes mellitus in infancy after enterovirus infections. *Diabet Med* 1998; **15**: 431-434 [PMID: 9609367 DOI: 10.1002/(SICI)1096-9136(199805)15: 5<431: : AID-DIA598>3.0.CO; 2-Q]

55 **Hyöty H**, Hiltunen M, Knip M, Laakkonen M, Vähäsalo P, Karjalainen J, Koskela P, Roivainen M, Leinikki P, Hovi T. A prospective study of the role of coxsackie B and other enterovirus infections in the pathogenesis of IDDM. Childhood Diabetes in Finland (DiMe) Study Group. *Diabetes* 1995; **44**: 652-657 [PMID: 7789630 DOI: 10.2337/diab.44.6.652]

56 **Muir P**, Singh NB, Banatvala JE. Enterovirus-specific serum IgA antibody responses in patients with acute infections, chronic cardiac disease, and recently diagnosed insulin-dependent diabetes mellitus. *J Med Virol* 1990; **32**: 236-242 [PMID: 1964475 DOI: 10.1002/jmv.1890320408]

57 **Honeyman MC**, Stone NL, Harrison LC. T-cell epitopes in type 1 diabetes autoantigen tyrosine phosphatase IA-2: potential for mimicry with rotavirus and other environmental agents. *Mol Med* 1998; **4**: 231-239 [PMID: 9606176]

58 **Honeyman MC**, Coulson BS, Stone NL, Gellert SA, Goldwater PN, Steele CE, Couper JJ, Tait BD, Colman PG, Harrison LC. Association between rotavirus infection and pancreatic islet autoimmunity in children at risk of developing type 1 diabetes. *Diabetes* 2000; **49**: 1319-1324 [PMID: 10923632 DOI: 10.2337/diabetes.49.8.1319]

59 **de Goffau MC**, Fuentes S, van den Bogert B, Honkanen H, de Vos WM, Welling GW, Hyöty H, Harmsen HJ. Aberrant gut microbiota composition at the onset of type 1 diabetes in young children. *Diabetologia* 2014; **57**: 1569-1577 [PMID: 24930037 DOI: 10.1007/s00125-014-3274-0]

60 **de Goffau MC**, Luopajärvi K, Knip M, Ilonen J, Ruohtula T, Härkönen T, Orivuori L, Hakala S, Welling GW, Harmsen HJ, Vaarala O. Fecal microbiota composition differs between children with β-cell autoimmunity and those without. *Diabetes* 2013; **62**: 1238-1244 [PMID: 23274889 DOI: 10.2337/db12-0526]

61 **Serena G**, Camhi S, Sturgeon C, Yan S, Fasano A. The Role of Gluten in Celiac Disease and Type 1 Diabetes. *Nutrients* 2015; **7**: 7143-7162 [PMID: 26343710 DOI: 10.3390/nu7095329]

62 **Sildorf SM**, Fredheim S, Svensson J, Buschard K. Remission without insulin therapy on gluten-free diet in a 6-year old boy with type 1 diabetes mellitus. *BMJ Case Rep* 2012; **2012**: [PMID: 22729336 DOI: 10.1136/bcr.02.2012.5878]

63 **Larizza D**, Calcaterra V, Klersy C, Badulli C, Caramagna C, Ricci A, Brambilla P, Salvaneschi L, Martinetti M. Common immunogenetic profile in children with multiple autoimmune diseases: the signature of HLA-DQ pleiotropic genes. *Autoimmunity* 2012; **45**: 470-475 [PMID: 22686660 DOI: 10.3109/08916934.2012.697594]

64 **Bakker SF**, Tushuizen ME, Stokvis-Brantsma WH, Aanstoot HJ, Winterdijk P, van Setten PA, von Blomberg BM, Mulder CJ, Simsek S. Frequent delay of coeliac disease diagnosis in symptomatic patients with type 1 diabetes mellitus: clinical and genetic characteristics. *Eur J Intern Med* 2013; **24**: 456-460 [PMID: 23414771 DOI: 10.1016/j.ejim.2013.01.016]

65 **Bakker SF**, Tushuizen ME, von Blomberg ME, Mulder CJ, Simsek S. Type 1 diabetes and celiac disease in adults: glycemic control and diabetic complications. *Acta Diabetol* 2013; **50**: 319-324 [PMID: 22539236 DOI: 10.1007/s00592-012-0395-0]

66 **Narula P**, Porter L, Langton J, Rao V, Davies P, Cummins C, Kirk J, Barrett T, Protheroe S. Gastrointestinal symptoms in children with type 1 diabetes screened for celiac disease. *Pediatrics* 2009; **124**: e489-e495 [PMID: 19706580 DOI: 10.1542/peds.2008-2434]

67 **Setty-Smith N,** Maranda L, Nwosu BU. Increased risk for vitamin D deficiency in obese children with both celiac disease and type 1 diabetes. *Gastroenterol Res Pract* 2014; **2014**: 561351 [DOI: 10.1155/2014/561351]

68 **Joshi AS,** Varthakavi PK, Bhagwat NM, Chadha MD, Mittal SS. Celiac autoimmunity in type 1 diabetes mellitus. *Arab J Gastroenterol* 2014; **15**: 53-57 [PMID: 25097046. DOI: 10.1016/j.ajg.2014.04.004]

69 **Mackinder M**, Allison G, Svolos V, Buchanan E, Johnston A, Cardigan T, Laird N, Duncan H, Fraser K, Edwards CA, Craigie I, McGrogan P, Gerasimidis K. Nutritional status, growth and disease management in children with single and dual diagnosis of type 1 diabetes mellitus and coeliac disease. *BMC Gastroenterol* 2014; **14**: 99 [PMID: 24885742 DOI: 10.1186/1471-230X-14-99]

70 **Warncke K**, Liptay S, Fröhlich-Reiterer E, Scheuing N, Schebek M, Wolf J, Rohrer TR, Meissner T, Holl RW. Vascular risk factors in children, adolescents, and young adults with type 1 diabetes complicated by celiac disease: results from the DPV initiative. *Pediatr Diabetes* 2016; **17**: 191-198 [PMID: 25677756 DOI: 10.1111pedi.12261]

71 **Camarca ME**, Mozzillo E, Nugnes R, Zito E, Falco M, Fattorusso V, Mobilia S, Buono P, Valerio G, Troncone R, Franzese A. Celiac disease in type 1 diabetes mellitus. *Ital J Pediatr* 2012; **38**: 10 [PMID: 24449104 DOI: 10.1186/1824-7288-38-10]

72 **Valentino R**, Savastano S, Tommaselli AP, Dorato M, Scarpitta MT, Gigante M, Lombardi G, Troncone R. Unusual association of thyroiditis, Addison s disease, ovarian failure and celiac disease in a young woman. *J Endocrinol Invest* 1999; **22**: 390-394 [PMID: 10401714]

73 **Myhre AG**, Aarsetøy H, Undlien DE, Hovdenak N, Aksnes L, Husebye ES. High frequency of coeliac disease among patients with autoimmune adrenocortical failure. *Scand J Gastroenterol* 2003; **38**: 511-515 [PMID: 12795461 DOI: 10.1080/00365520310002544]

74 **Elfström P**, Montgomery SM, Kämpe O, Ekbom A, Ludvigsson JF. Risk of primary adrenal insufficiency in patients with celiac disease. *J Clin Endocrinol Metab* 2007; **92**: 3595-3598 [PMID: 17595243 DOI: 10.1210/jc.2007-0960]

75 **Van den Driessche A**, Eenkhoorn V, Van Gaal L, De Block C. Type 1 diabetes and autoimmune polyglandular syndrome: a clinical review. *Neth J Med* 2009; **67**: 376-387 [PMID: 20009114]

76 **Lakhotia M**, Pahadia HR, Kumar H, Singh J, Tak S. A Case of Autoimmune Polyglandular Syndrome (APS) Type II with Hypothyroidism, Hypoadrenalism, and Celiac Disease - A Rare Combination. *J Clin Diagn Res* 2015; **9**: OD01-OD03 [PMID: 26023582 DOI: 10.7860/JCDR/2015/10755.5748]

77 **Matsueda K**, Rosenberg IH. Malabsorption with idiopathic hypoparathyroidism responding to treatment for coincident celiac sprue. *Dig Dis Sci* 1982; **27**: 269-273 [PMID: 7075423 DOI: 10.1007/BF01296927]

78 **Saha S,** Saini S, Makharia GK, Datta Gupta S, Goswami R. Prevalence of celiac disease in idiopathic hypoparathyroidism and effect of gluten-free diet on calcemic control. *Clin Endocrinol* (Oxf) 2016; **84**: 578-586 [PMID: 26147910 DOI: 10.1111/cen.12850]

79 **Hrubisková K**, Jackuliak P, Vanuga P, Pura M, Payer J. [Autoimmune polyendocrine syndrome type 2 associated with autoimmune hypophysitis and coeliac disease]. *Vnitr Lek* 2010; **56**: 1169-1176 [PMID: 21250496]

80 **Delvecchio M**, De Bellis A, Francavilla R, Rutigliano V, Predieri B, Indrio F, De Venuto D, Sinisi AA, Bizzarro A, Bellastella A, Iughetti L, Cavallo L. Anti-pituitary antibodies in children with newly diagnosed celiac disease: a novel finding contributing to linear-growth impairment. *Am J Gastroenterol* 2010; **105**: 691-696 [PMID: 19904244 DOI: 10.1038/ajg.2009.642]

81 **Meazza C**, Pagani S, Laarej K, Cantoni F, Civallero P, Boncimino A, Bozzola M. Short stature in children with coeliac disease. *Pediatr Endocrinol Rev* 2009; **6**: 457-463 [PMID: 19550380]

82 **Giovenale D**, Meazza C, Cardinale GM, Sposito M, Mastrangelo C, Messini B, Citro G, Delvecchio M, Di Maio S, Bozzola M. The prevalence of growth hormone deficiency and celiac disease in short children. *Clin Med Res* 2006; **4**: 180-183 [PMID: 16988097 DOI: 10.3121/cmr.4.3.180]

83 **Kapur G**, Patwari AK, Narayan S, Anand VK. Serum prolactin in celiac disease. *J Trop Pediatr* 2004; **50**: 37-40 [PMID: 14984168 DOI: 10.1093/tropej/50.1.37]

84 **Delvecchio M**, Faienza MF, Lonero A, Rutigliano V, Francavilla R, Cavallo L. Prolactin may be increased in newly diagnosed celiac children and adolescents and decreases after 6 months of gluten-free diet. *Horm Res Paediatr* 2014; **81**: 309-313 [PMID: 24603159 DOI: 10.1159/000357064]

85 **Freeman HJ**. Infertility and ovarian failure in celiac disease. *World J Obstet Gynecol* 2015; **4**: 72-76 [DOI: 10.5317/wjog.v4.i4.72]

86 **Singh P**, Arora S, Lal S, Strand TA, Makharia GK. Celiac Disease in Women With Infertility: A Meta-Analysis. *J Clin Gastroenterol* 2016; **50**: 33-39 [PMID: 25564410 DOI: 10.1097/MCG.0000000000000285]

87 **Bakker SF**, Tushuizen ME, von Blomberg BM, Bontkes HJ, Mulder CJ, Simsek S. *Diabetol Metab Syndr* 2016; **8**: 51 [PMID: 27478507 DOI: 10.1186/s13098-016-0166-0]

88 **Zhao Z**, Zou J, Zhao L, Cheng Y, Cai H, Li M, Liu E, Yu L, Liu Y. Celiac Disease Autoimmunity in Patients with Autoimmune Diabetes and Thyroid Disease among Chinese Population. *PLoS One* 2016; **11**: e0157510 [PMID: 27427767 DOI: 10.1371/journal.pone.0157510]

**P-Reviewer:** Holmes GKT, Jafari SA, Nenna R, Ribaldone DG, Tarnawski AS

**S-Editor:** Qi Y **L-Editor: E-Editor:**

**Specialty type:** Gastroenterology and hepatology

**Country of origin:** Canada

**Peer-review report classification**

Grade A (Excellent): A

Grade B (Very good): B, B

Grade C (Good): C

Grade D (Fair): D

Grade E (Poor): 0