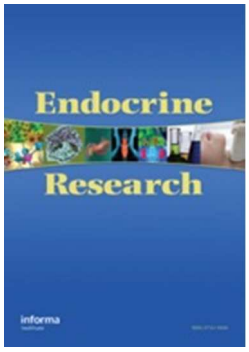

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Endocrine Complications of Celiac Disease: A Case Report and Review of the Literature

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Abstract

Celiac disease (CD) is an autoimmune disorder characterized by intestinal inflammation in response to gluten. CD can cause a wide range of extra-intestinal complications, including endocrine manifestations. Metabolic bone disease including osteoporosis and osteopenia, vitamin D deficiency, secondary hyperparathyroidism and less frequently osteomalacia can be seen. CD is also associated with other endocrine disorders including, hypo- and hyperthyroidism, type 1 diabetes, adrenal insufficiency, ovarian failure and infertility, androgen insensitivity, impaired growth and growth hormone deficiency and autoimmune polyendocrine syndromes. This review will summarize recent literature regarding endocrine disorders related to CD.

Case Report

A 60 year old man presented for endocrine evaluation due to a four year history of fatigue, reduced muscle mass and strength, loss of libido, mild cognitive changes, depressive symptoms, and weight loss of twenty pounds. Prior initial outside evaluation indicated an elevated total testosterone level. The patient reported loss of appetite and constipation but no vomiting, diarrhea, abdominal pain or food intolerance. Colonoscopy, three years prior, had been normal. He was the biological father of two sons ages 30 and 27 and reported no other symptoms of hypogonadism. He described one inch of height loss without history of fracture and did not smoke or consume alcohol. He had been on varying antiepileptic drugs for thirty years following a generalized tonic-clonic seizure associated with a right temporal subarachnoid cyst, which was stable on serial imaging. At presentation, his medications included divalproex and vitamin D.

On examination, the patient was thin (148.6 pounds) but otherwise euthyroid-appearing with a normal adult male phenotype and body mass index (BMI) 22.1 kg/m^2. The thyroid gland

was normal in size with irregular texture. There was no kyphosis or gynecomastia. Abdominal exam was normal. Circumcised phallus and testes were normal, the latter measuring 4.5x3.0 cm each. On laboratory testing, serum glucose, renal, liver and thyroid function, electrolytes, calcium, albumin, alkaline phosphatase, and morning cortisol levels were all normal. Hemoglobin and hematocrit were borderline low to frankly low with normal iron studies and vitamin B12 level. Serial endocrine testing (Mayo Clinic Laboratories, Rochester, MN) revealed total testosterone ranging from 1030-1120 ng/dl (adult male reference range: 240-950 ng/dl), free testosterone 9.0-15.5 ng/dl (ref: 9-30), luteinizing hormone (LH) 37.3-46.6 mIU/ml (ref: 1.9-9.3), follicle stimulating hormone (FSH) 19.6-22.9 mIU/ml (ref: 1.4-18.1), sex hormone-binding globulin (SHBG) 145-160 nmol/l (ref: 10-60), prolactin 3.8 ng/ml (ref: 2.1-17.7), estradiol < 11.8 pg/ml (ref: 11.6-41.2), and inhibin B 320 pg/ml (ref: <399).

As the patient's symptoms were consistent with hypogonadism, free testosterone levels were generally in the lower reference range (despite elevated total testosterone with high SHBG levels) and gonadotropins were elevated, a trial of transdermal testosterone was initiated. Over one year, testosterone supplementation with titration had no effect on the patient's symptoms, weight or total or free testosterone; in contrast, LH and FSH fell to 16.8 and 13.6 mIU/ml, respectively, with SHBG 116 nmol/l (following a change of divalproex to phenytoin).

Dual energy x-ray absorptiometry (DXA; Lunar Prodigy, GE Healthcare, Madison, WI), one year after testosterone initiation, revealed osteoporosis with T-scores of -5.2, -3.8 and -4.3 at the lumbar spine, hip and 1/3 radius, respectively. Metabolic bone disease evaluation indicated secondary hyperparathyroidism: intact parathyroid hormone (iPTH) 155 pg/ml (ref: 14-72) with normal total (9.5 mg/dl; ref: 8.4 - 10.5) and ionized (4.8 mg/dl; ref: 4.6-5.4) calcium levels, albumin (4.7 g/dl; ref: 3.1-4.7), and renal function. Total alkaline phosphatase (220 U/l; ref: 20–

150) and bone-specific alkaline phosphatase (35 mcg/l; ref: 0-20) were consistent with osteomalacia. Phosphorus (4.0 mg/dl; ref: 2.4-5.0) and 25-hydroxyvitamin D (35 ng/ml) on supplementation were normal, while $1,25(OH)_2$ vitamin D was elevated (78 pg/ml; ref: 18–64); 24-hour urine (total volume 2550 ml and creatinine 1.4 g) calcium was undetectable (<26 mg; ref: 100-250), whereas urine n-telopeptide (NTX) was elevated (209 nmol BCE/mmol creatinine; ref: 21-66).

Celiac disease (CD) serologies were equivocally positive in the setting of IgA deficiency (total IgA 9 mg/dl; ref: 61-356): tissue transglutaminase (tTG) IgA 5.4 U/ml (<4.0 negative) and deamidated gliadin IgG 19.6 U (<20.0 negative); human leukocyte antigen (HLA) testing was positive for DQ2 alleles associated with CD. A duodenal biopsy by endoscopy showing severe villous atrophy and lymphocytosis confirmed CD. The diagnosis of CD with metabolic bone disease and androgen resistance was made two years after referral to endocrinology and six years after symptom onset.

A gluten-free diet (GFD) was initiated and rigorously maintained. Successive biopsies revealed duodenal mucosal healing by fourteen months on GFD. Constitutional symptoms and constipation improved and the patient gained 20 pounds after three years on GFD. Bone mineral density (BMD) increased over two years by 36.5%, 21.8% and 14.2% at the spine, hip and 1/3 radius, respectively, while on a GFD with supplemental calcium and vitamin D. Within the same period, metabolic bone indices normalized: iPTH 47.5 pg/ml, alkaline phosphatase 69 U/l, 25OH vitamin D 55 ng/ml, 24-hour urine calcium 80-164 mg/24 hrs, and urine NTX 32 nmol BCE/mmol creatinine. During the first sixteen months of GFD and on tapering testosterone supplementation, both LH and FSH normalized (5.6 and 8.1 mIU/ml, respectively), while SHBG decreased to 83 nmol/l without a change in total and free testosterone.

Subsequently on continued GFD without testosterone, LH and FSH rose (22.8 and 22.3 mIU/ml, respectively) without changes in total or free testosterone or SHBG. Notwithstanding multiple confounders, the serial changes in gonadotropins and SHBG were interpreted as incomplete androgen insensitivity partially alleviated by GFD. On GFD, the patient remained euthyroid with mildly elevated thyroid peroxidase antibodies up to 44.5 IU/ml (ref: <9.0) and stable, bilateral sub-centimeter thyroid nodules by ultrasound. Due to T-scores remaining in the osteoporotic range, the patient was treated with teriparatide followed by zoledronic acid.

Introduction

Celiac disease is an autoimmune disorder characterized by intestinal inflammation in response to gluten, a family of proteins found in wheat, barley and rye. Classic CD is characterized by malabsorption, diarrhea and weight loss, though today many patients have only minor gastrointestinal symptoms and can be asymptomatic. CD can also cause a wide range of extra-intestinal complications, including endocrine manifestations (1). Metabolic bone disease including osteoporosis and osteopenia, vitamin D deficiency, secondary hyperparathyroidism and less frequently osteomalacia can be seen. CD is also associated with other endocrine disorders including, hypo- and hyperthyroidism, type 1 diabetes, adrenal insufficiency, ovarian failure and infertility, androgen insensitivity, impaired growth and growth hormone deficiency and autoimmune polyendocrine syndromes. This review will summarize endocrine disorders related to CD with a focus on recent investigations where available.

Epidemiology, Pathogenesis and Diagnosis

CD has an estimated prevalence of 1% worldwide (2, 3); it is more common in Caucasians of European ancestry and less frequent among African-Americans and Hispanic-Americans (4). Even within individual European countries, the prevalence can vary considerably (3). Less is known about the prevalence of CD in individuals of Asian descent, though CD is common in northern India (5). Both in the United States and Western Europe the prevalence of CD has increased since the 1950's, likely due to a combination of increased global incidence, increased patient and physician awareness, and increases in CD diagnosis (2, 6-8).

While classically thought of as a disease of children, CD can be diagnosed at any age, and both children and adults are affected at similar rates (8). There is a female predominance of the disease, though this may be due to disparities in diagnosis as opposed to an inherent feature of the disease (9). CD has a strong genetic basis - 90% of individuals with CD carry a particular HLA genotype, HLA-DQ2, and the remaining carry HLA-DQ8 (2, 10). Nevertheless, not all individuals who are positive for HLA-DQ2 or HLA-DQ8 develop CD upon exposure to gluten, and so genes outside of the HLA loci and non-dietary environmental factors are thought to contribute to the pathogenesis (2, 10). Recent investigations point to the possible role of the gut microbiome in contributing to development of CD (11).

Individuals with CD develop an immune response to the ingestion of gluten, specifically its peptide component gliadin. In the intestinal lamina propria, the enzyme tissue transglutaminase (tTG) deamidates gliadin, enabling its binding to HLA-DQ2 or HLA-DQ8 molecules on antigen presenting cells and presentation to CD4+ T cells (10). Pro-inflammatory cytokines and autoantibodies are subsequently produced in this adaptive immune response. The innate immune system is also involved and is reflected in the increase in intraepithelial lymphocytes, which express natural killer T-lymphocyte receptors (10). It is unclear how the

adaptive lamina propria immune response and the intraepithelial innate immune reactions relate to each other, but it is apparent that all are required for the "full blown" intestinal celiac lesion characterized by villous atrophy and intraepithelial lymphocytosis (1, 2, 10).

Diagnosis of CD relies on a combination of testing for elevated concentrations of autoantibodies and duodenal biopsy showing villous atrophy and intraepithelial lymphocytosis (2). Autoantibodies used in screening include IgA-tTG, which has a high sensitivity and negative predictive value, as well as IgA endomysial antibodies (EMA) and IgA and IgG deamidated gliadin peptides (2, 12). In adults, it is generally recommended that serologic testing for CD be performed first, and then if positive, the diagnosis should be confirmed by duodenal biopsy (2). In the pediatric population, recent European guidelines allow for serological diagnosis without biopsy confirmation in some cases (13). Following diagnosis, patients with CD are instructed to adhere to a life-long gluten-free diet (GFD), which is the only currently available treatment.

Metabolic Bone Disease

Metabolic bone disease is a frequent complication of CD and sometimes the presenting manifestation. Multiple reports suggest that osteopenia and osteoporosis are common in CD and screening with DXA is recommended at diagnosis (14). There is, however, a wide range of prevalence estimates described, varying from 9-75% (15-18). Low BMD can occur in both those with and without gastrointestinal symptoms, such as diarrhea (16, 19, 20). Data regarding fracture risk in patients with CD is conflicting but a recent meta-analysis of prospective studies indicated that CD was associated with a 30% increase in the risk of any fracture and a 69% increase in the risk of hip fracture (21-25). Another recent study suggests CD is associated with an increased fracture risk assessment (FRAX) score, implying it is an independent risk factor for

fracture (20).

Recent advances in skeletal imaging, including the development of high resolution peripheral quantitative computed tomography (HRpQCT), have allowed insight into the pathogenesis of skeletal fragility in CD. A recent HRpQCT study in adult women with CD indicated low trabecular volumetric BMD and fewer, more widely and irregularly spaced trabeculae at both the radius and tibia as well as thinner cortices at the tibia versus controls (26). These microstructural deficits led to lower whole-bone stiffness and failure load in CD patients at both skeletal sites, which would predispose to an increased risk of fracture. A similar study in premenopausal women likewise found trabecular deficits and lower cortical density at both skeletal sites but no difference in cortical thickness (27). The latter study also suggested that those with symptomatic versus asymptomatic CD had greater microstructural deterioration (27).

The pathogenesis of reduced BMD, microarchitectural deterioration and increased skeletal fragility in CD remains incompletely investigated, but both local and systemic mechanisms have been implicated (14, 28). While metabolic bone disease is one of the most frequent complications of CD, few studies have directly investigated the mechanism and more research is needed in this area. Weight loss, general malnutrition and hypogonadism may contribute to bone loss in some CD patients. A major mechanism, however, is thought to be villous atrophy in the small bowel, the major site of calcium and vitamin D absorption. In some cases, malabsorption of calcium and vitamin D may lead to compensatory secondary hyperparathyroidism and bone resorption to maintain normal serum calcium levels (14, 19, 28). Although there are limited data regarding the prevalence of secondary hyperparathyroidism in CD, one study indicates it is present in 28% of patients and that PTH level is negatively associated with BMD at the forearm (29). A second study suggested a prevalence of 25% in

newly diagnosed patients as well as those refractory to treatment while the rate was 19% in those who were responsive to treatment (30). In some cases, prolonged secondary hyperparathyroidism can evolve into autonomous parathyroid function and primary hyperparathyroidism (PHPT). A recent study suggests that CD patients are at almost twice the risk for PHPT (31). Osteomalacia may be present in some patients due to prolonged vitamin D deficiency and calcium malabsorption, though it appears to be rare today (32).

Another contributor to bone loss in CD may be the underlying autoimmune and inflammatory component of CD. CD increases serum levels of pro-inflammatory cytokines interleukin-1 and 6 and tumor necrosis factor-alpha, which could increase the ratio of receptor activator of nuclear factor kappa B ligand (RANKL) to osteoprotegerin (OPG) (14, 33). High RANKL/OPG ratios increase the maturation and activation of osteoclasts, which are responsible for bone resorption. There are limited data regarding whether OPG or RANKL levels are altered in patients with CD, though one report indicates that the OPG/RANKL ratio is lower in CD patients than in controls and was positively correlated with spine BMD (34). Another study demonstrated OPG neutralizing antibodies are present in some patients with CD (35).

With institution of and adherence to a GFD, BMD tends to improve in CD patients, with much of the recovery taking place in the first year (36-45). There is considerable intra-individual variability, however, and little data about which patients have the greatest capacity for skeletal recovery. Some data suggest improvement only in symptomatic CD while another study showed similar degrees of BMD recovery in those without symptoms (19, 38). Other studies suggest that improvement depends on menopausal status or age (38, 42, 43, 46). A recent study in a large celiac cohort suggested that those with the lowest serum calcium had the greatest BMD increase after diagnosis consistent with calcium malabsorption influencing the potential for recovery (32).

Despite improvement, however, GFD adherence may not completely restore BMD and increased fracture risk persists even after institution of a GFD (16, 25, 37, 41, 47). Recent data suggest those with persistent villous atrophy remain at increased risk after treatment compared to those with mucosal healing (23, 28, 48). A 2017 study found that more severe Marsh histopathological stage, a system of measuring severity of intestinal damage in CD, was associated with low BMD (49).

There are almost no data assessing the effect of pharmacological osteoporosis treatment specifically in patients with CD (50). In the absence of data, it is reasonable to consider treatment in postmenopausal women and men > age 50 with osteoporosis that does not improve on a GFD, those with a fragility fracture or those at high risk of fracture, based on National Osteoporosis Foundation (NOF) guidelines. Parenteral agents may theoretically be more appealing due to the possibility of inadequate absorption of bisphosphonates in the setting of CD. However, anti-resorptives are contraindicated in those with hypocalcemia, vitamin D deficiency or osteomalacia and can precipitate or worsen hypocalcemia (51). Mineral metabolism abnormalities, including secondary hyperparathyroidism, should be corrected prior to initiation of therapy.

Association with Other Endocrine Diseases

Thyroid Disease

Both hypo- and hyperthyroidism have been associated with CD. The link between autoimmune thyroid disease (AIT) and CD is incompletely understood but is likely due in part to HLA genotypes predisposing to both conditions. HLA-DQ2 and DQ8 are associated with both CD and AIT (52). Non-HLA loci have been implicated as well. Variants in the gene encoding cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4), which serves as an immune checkpoint

and downregulates immune responses, have also been linked to both CD and AIT disease (53-55). Inconsistent data indicate adherence to a GFD may reduce the risk of developing additional autoimmune disorders suggesting that uncontrolled chronic inflammation could also play a role in promoting more generalized endocrine autoimmunity (56, 57). Anti tTG antibodies binding to tissue transglutaminase in the thyroid gland have been suggested as an etiological factor (58).

The prevalence of hypothyroidism is reported to be 2-13% in patients with CD in several studies equating to about a 3- to 4-fold higher risk than in the general population or controls (59-61). Individual studies have conflicting results with regard to whether the risk of hyperthyroidism is increased (59, 60, 62). The largest study to date (which included 14,021 CD patients) was conducted in Sweden (62). This analysis found the risk of hypothyroidism, thyroiditis and hyperthyroidism to be increased by 2.9-4.4 fold compared to controls (62). The risk of thyroid dysfunction was highest in children with CD (62). Other studies have confirmed an increased risk of hypothyroidism in children and young adults with CD (63). Multiple studies suggest an increased risk of positive thyroid antibodies with normal thyroid function among CD patients as well (60, 61). Work in patients without CD suggests that such antibody positive patients tend to have an increased risk for developing future thyroid dysfunction (64).

Longitudinal data regarding the effect of GFD upon thyroid function are limited (60, 65). One study concluded that strict adherence to a GFD may "normalize subclinical hypothyroidism" (60) while the other did not (65). In the first, there was, however, no comparison to controls without CD, making it impossible to determine whether normalization of thyroid function was related to treatment or the natural history of subclinical hypothyroidism, which tends to resolve spontaneously in a sizable percentage of patients (66).

A recent meta-analysis confirmed that patients with CD are at 3-fold increased risk for thyroid disease (defined as hypo- or hyperthyroidism or positive thyroid antibodies) compared to controls (61). In this analysis, risk of hypothyroidism and euthyroidism with positive antibodies was increased by 3.38 (95% CI 2.88-6.56) and 4.35 (95% CI 2.88-6.56) times, respectively; in contrast, there was no increased risk of hyperthyroidism and risk of thyroid disease was not lower in those who were on a GFD compared to those who were not (61).

Given the increased risk for hypothyroidism demonstrated in these studies, it is reasonable to screen patients with CD for thyroid dysfunction. Both the American Thyroid Association and the American Association of Clinical Endocrinologists recommend measurement of thyroid function in those with autoimmune diseases (67). On the contrary, the prevalence of CD is also increased in those with AIT. Some experts recommend screening for CD in those with AIT, though this is not uniformly endorsed by guidelines (68, 69). Suspicion for CD should be raised in patients with hypothyroidism who are compliant with levothyroxine but refractory to treatment, as CD can cause malabsorption of levothyroxine (70). One study suggested that hypothyroid patients requiring higher daily doses of levothyroxine are more likely to have CD. The authors of this study recommended hypothyroid patients requiring ≥125mcg/day of levothyroxine undergo serologic testing for CD (71).

Type 1 Diabetes Mellitus (T1DM)

The same mechanisms that predispose CD patients to AIT are thought to contribute to the development of T1DM. The prevalence of biopsy-diagnosed CD in children with TIDM ranges from 1.6% to 12.3% (72, 73). A 2014 systematic review with a meta-analysis identified 27 English language studies, each containing over 100 patients with TIDM, who underwent

screening for CD with confirmatory duodenal biopsy (74). Among 26,605 Type I diabetics, the estimated pooled prevalence of CD was 6% (95% CI 5.0-6.9), though there was significant heterogeneity which was not explained by subgroup analyses (74). CD prevalence decreased with age at testing, with the highest CD prevalence among children (6.2%)(74).

Due to this elevated risk, screening for CD among patients with TIDM is recommended by some societies and guidelines (2, 75); however, the ideal timing for screening has not been determined. As a result of varying recommendations about CD screening in TIDM, practice patterns vary (76). In a systematic review of 9 longitudinal studies containing 11,157 children with TIDM, 43.4 patients per 1,000 patient-years were diagnosed at 1 year, 32.8 at 2 years, and 20.1 at 5 years (77). The authors concluded that screening for CD should be considered at TIDM diagnosis and within 2 and 5 years thereafter (77). In the same study, investigators found 7% of CD diagnoses occurred before the diagnosis of T1DM (77). Few studies, however, specifically evaluated the risk of TIDM in patients with CD. A Swedish prospective study, showed that children with CD are at increased risk (hazard ratio [HR] 2.4) for the subsequent development of TIDM before age 20, though the absolute risk was low (78). A later Italian study did not confirm this but was much smaller and may have been underpowered (63).

The benefit of a GFD on glycemic control and cardiovascular risk in those with coexisting TIDM and CD is unclear, as there are few longitudinal studies. One risk factor that has been shown to fairly consistently improve with institution of a GFD is high-density lipoprotein (HDL); this may be because the intestine is a major source of apo A1 (79, 80). Indeed, one study reported that both glycosylated hemoglobin (HbA1c) and HDL improved in GFD-adherent compared to non-adherent patients one year after GFD initiation (81). It is unclear, however, if this is due to a GFD or better medical compliance in general among

adherers. In contrast, another study showed an increase in HDL, but not lower HbA1c, 1 year after GFD adherence (82). Studies also suggest there is an increased risk of long-term diabetes-related complications, including mortality and microvascular disease in those with TIDM and CD compared to those with TIDM alone, though GFD adherence was not assessed (83-85).

Type 2 Diabetes (T2DM)

The literature exploring the relationship between CD and T2DM is limited, but most data indicate no increased risk for T2DM and a possible protective effect of CD. A 1998 study of 745 patients with non-insulin dependent diabetes found CD in 0.27% (86). In 2013, a US study among 840 CD patients demonstrated a lower prevalence of non-insulin dependent diabetes (3.1% vs. 9.6%) and metabolic syndrome compared to matched controls (3.5 vs. 12.7%) (87). These results remained significant even when adjusting for BMI and smoking (87). The authors suggest that CD patients may be protected against the development of non-insulin dependent diabetes, though a possible mechanism remains to be determined (87). In contrast, a Finnish study reported the prevalence of T2DM was 2.8% in 1,358 patients with CD, which was similar to population-based values (88). However, a 2017 study evaluating the presence of IgA-tTG with confirmatory biopsy for CD in patients with T2DM on insulin therapy with poor glycemic control found CD in 1.45%, which is slightly higher than the 1% prevalence of CD worldwide (89). Patients with T2DM who had lower C-peptide values also had higher levels of IgA-tTG (89). The authors suggested that T2DM patients with poor glycemic control on insulin therapy who have low C-peptide levels may benefit from CD testing (89).

Adrenal Disease

Autoimmune adrenal (Addison's) disease has been associated with CD in a handful of studies. A large Swedish study found that patients with CD were at an astonishing 11.4 times the risk for developing Addison's disease; increased risk was observed in both children and adults (90). The prevalence in CD patients was 0.25% versus 0.02% in those without CD. Most other studies have assessed the prevalence of CD in patients with Addison's disease. One study found 12.2% of patients with Addison's disease had CD (91). In a Norwegian study, the prevalence of CD among 76 patients with Addison's disease identified via a registry was 7.9%. (92). An Italian study suggested a CD rate of 5.9% in 17 patients with Addison's disease (93). Similar mechanisms predisposing to other autoimmune endocrine conditions in patients with CD likely also affect risk for autoimmune adrenal disease. In one study, those with Addison's disease and CD were all positive for the CD-associated HLA haplotype DR3-DQ2 (92).

Hypogonadism and Infertility

Female Hypogonadism, Reproductive Disorders and Obstetric Complications

CD has been associated with female reproductive disorders, including delayed menarche, early menopause, and amenorrhea (94). Patients with CD have been reported to have later mean age of menarche compared to those with irritable bowel syndrome (IBS; 13.7 ± 1.5 vs 12.8 ± 1.6 years), though age at menopause did not differ (95). Secondary amenorrhea was present in 28% of women with CD, but none of those with IBS (95). Subgroup analyses suggested some relationship to nutritional status. In contrast, another study found no difference in menarche age between women who had menarche before vs. after the diagnosis of CD, nor did menarche age differ compared with their mothers or healthy controls (96). A 2011 study suggested that compared to healthy controls, women with untreated CD, had lower BMI and a shorter fertile

lifespan due to later menarche and earlier menopause (97). In 2014, another study found that 24% of women with CD had dysfunctional uterine bleeding compared with 10% of controls; 83.3% of patients had normalization of menses after 3 months of a GFD (98). Although studies are small and mostly based on historical information, they suggest CD may be associated with later menarche and amenorrhea; further research is needed in this area.

Infertility has also been reported to be a feature of CD. A 2016 meta-analysis reported a pooled CD prevalence of 2.3% (95% CI 1.4-3.5) among 884 women with infertility and a 3.2% (95% CI 2.0-4.1) prevalence among 623 women with unexplained infertility (99). Compared to controls, women with infertility had 3.5 times the odds of having CD (95% 1.3-9.0) and women with unexplained infertility had 6 times the odds of having CD (95% CI 2.4-14.6) (99). In contrast, no increased risk of infertility was found in two large population-based cohort studies of women with CD, one performed among 1,521 women in the UK (HR 1.01, 95% CI 0.91-1.14) and the other performed among 11,495 women with CD in Sweden (HR 1.03, 95% CI 1.01-1.05) (100, 101). However, the latter study reported decreased fertility 0-2 years before the diagnosis of CD (HR 0.63; 95% CI 0.57-0.70) (101). Similarly, a 2014 meta-analysis reported 3.09 times higher odds of undiagnosed CD among women with infertility (95% CI 1.74-5.49), though no difference in the odds of diagnosed CD existed (OR 0.99, 95% CI 0.86-1.13) (102). These data suggest that women with infertility, particularly if unexplained, should be screened for CD. Because available data tend to suggest that there is no increased infertility in those with diagnosed CD, they imply that treatment of CD may restore reproductive function. Prospective longitudinal studies are needed, however, to confirm this.

In women with CD who become pregnant, spontaneous abortion and several obstetrical complications have been reported to be higher in comparison to those without CD (103, 104). A

recent study indicated those with recurrent pregnancy loss, were more likely have CD-associated haplotype DQ2/DQ8 compared to controls (105). Obstetrical complications have been assessed recently in a 2016 meta-analysis that included 10 cohort studies and 4.8 million women (104). It indicated women with CD had a significantly higher risk for the development of preterm birth, intrauterine growth restriction, still birth, low birthweight and small for gestational age infants (104). Risk for preeclampsia was not increased. Subgroup analyses suggested that women with diagnosed and treated CD had a lower risk for preterm birth compared to those with undiagnosed and untreated CD, indicating that adherence to a GFD could alter the risk of this complication.

The mechanisms causing reproductive dysfunction in CD have been inadequately investigated to date and remain to be elucidated. Most studies have not assessed hormonal regulators of reproductive function. Nutritional deficits may play a role. Zinc and selenium deficiencies have been linked to impaired synthesis and secretion of FSH and LH (106), and have been reported in children with untreated CD (107, 108). Degree of malnutrition and low weight may contribute to delayed menarche and secondary amenorrhea in CD, as they do in other conditions (95). Only one study to date has evaluated pituitary gland function in women with CD. This 2018 study failed to show altered values of LH, FSH, and prolactin in 46 women with CD, but did report decreased anti-Mullerian hormone (AMH), an indicator of declining ovarian function and follicular reserve (109). Given this study's small sample size (109), larger studies evaluating gonadotropins and sex hormones in women with CD are warranted. Other studies suggest that infertility may be caused by anti-tTG antibodies binding to trophoblastic cells and/or endometrial endothelial cells leading to placental damage (110-112). These mechanisms could explain the increased risk of miscarriage, low birth weight, and preterm delivery demonstrated in pregnant women with CD (112).

Male Hypogonadism

Fewer studies have focused on male reproductive disorders in CD, but case reports of hypogonadism can be found as early as the 1950's (113). A small study from the 1980's comparing 28 men with CD to 19 men with Crohn's disease reported increased rates of hypogonadism (7 vs. 0%) and sexual dysfunction in CD compared to controls (114). Males with CD also had abnormal sperm morphology and motility. Sperm morphology improved after gluten withdrawal (114). Additionally, infertility was reported in 19% of males with CD in this study (114). Sperm impairment was unrelated to nutritional deficiencies, including B12 and folate, or to infertility.

Results from a large population-based cohort study of 7,121 Swedish men with biopsy-verified CD from 2011, however, are reassuring, as there was no significant increase in infertility (HR of 1.02 (95% CI 0.99–1.04) (115). Rates of CD among men reporting infertility have also been investigated. Two studies of couples with infertility found a CD prevalence of 0.39-1% among males (116, 117), while a third found a higher prevalence of 6% (118). A meta-analysis of two of these studies (116, 118), however, reported no increased odds of CD in this group (OR 1.63, 95% CI 0.60-4.46). The majority of these patients were diagnosed by serology only (102).

Small studies of men with CD from the 1970's and 1980's have reported androgen resistance, characterized by increased basal FSH and LH (119-121), increased plasma testosterone and free testosterone index (120, 121), elevated plasma SHBG (121), exaggerated gonadotropin responses to LH-releasing hormone (119), and reduced dihydrotestosterone (DHT) in men with CD (120, 121). These abnormalities were not present in controls with Crohn's disease who had similar nutritional status (120, 121). Available data suggest that treatment with a

GFD alleviates androgen insensitivity; in several studies, laboratory abnormalities (with the exception of increased basal and stimulated FSH values) returned to normal with healing of jejunal morphology after initiation of a GFD (119-121). Elevated prolactin values have also been reported in men (119) and children with untreated CD (122, 123); however, these values were only moderately elevated and have not been associated with impotence or infertility (119). Despite no apparent risk of male infertility in CD overall, further studies are needed to verify if there is any association between CD and pituitary or peripheral regulation of gonadal function.

Growth Hormone Deficiency and Growth

Short stature or failure to thrive can be the presenting sign of CD in children (124-126). Most children with CD and short stature display "catch up" growth when a GFD is instituted (126). A subset of children may also have transient functional growth hormone deficiency (GHD), growth hormone resistance or low insulin-like growth factor-1 (IGF-1) that reverses with institution of a GFD (127). One study indicated that among children with short stature, 0.63% had CD and 0.23% had both CD and GHD (128). Lack of an increase in growth velocity after adherence to a GFD should raise suspicion that GHD may be congenital and/or permanent (126, 129, 130). One study indicated that those who responded to a GFD with an appropriate increase in growth velocity had more delayed bone age than non-responders, suggesting this could be helpful in determining who may be most likely to respond (130). Treatment with growth hormone in combination with a GFD can increase growth rate in children with GHD and CD (126, 128, 131). Final adult height in CD patients is typically similar to that of the general population, unless there is a delay in diagnosis (132, 133).

One study suggested that 25% of adults with CD may have complete or partially impaired growth hormone secretion that is independent from diagnosis and implementation of a GFD (134). All those with GHD were men and none had anti-pituitary antibodies (APA) (134). Conversely, a high percentage (42%) of APA antibodies has been reported in children newly diagnosed with CD compared to only 2% of controls without CD (135). IGF-1 was lower in patients who were APA positive compared to those who were APA negative and height was positively correlated with IGF-1 (135).

Autoimmune Polyendocrine Syndromes

CD may occur as part of an autoimmune polyendocrine syndrome (APS), a rare collection of disorders characterized by the autoimmune failure of two or more endocrine glands. APS type 1 (APS-1), also known as autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy (APECED), is a rare autosomal recessive condition due to a mutation in the autoimmune regulator (*AIRE)* gene; it is characterized by the development of two of three manifestations, including chronic mucocutaneous candidiasis, hypoparathyroidism, and Addison's disease, during childhood (136). CD is not a feature of APS-1.

On the other hand, APS type 2 (APS-2), a more common, polygenic condition presenting in adolescence or adulthood, is characterized by at least two of three endocrinopathies: Addison's disease, TIDM and thyroid disease (136, 137). CD can be a feature of APS-2 along with other non-endocrine autoimmune conditions such as alopecia, vitiligo and pernicious anemia (136-140). Primary ovarian failure has also been described. APS-2 is a clinical diagnosis supported by the presence of auto-antibodies against thyroid peroxidase, glutamic acid decarboxylase 65, and to 21-hydroxylase (136). Though some suggest further subcategorizing

APS-2 without adrenal involvement as APS-3 and CD has been reported in the literature in association with APS-3, it is not clearly recognized as a separate entity (141, 142).

Patients with concomitant APS-2 and CD have been found to harbor variants in haplotypes DR3-DQ2 and DR4-DQ8 which have also been associated with TIDM, AIT, and Addison's disease in other studies, indicating a common genetic predisposition (136, 143-145). A 2016 study found that patients with "APS-3" had a higher frequency of positive tTG antibodies (36%) compared to patients with TIDM or AIT alone, though this study only tested for CD autoimmunity and not biopsy-confirmed CD (146).

As noted in prior sections, CD can occur in conjunction with autoimmune failure of one or more endocrine glands (including the thyroid, pancreas or adrenal), outside of the context of an APS syndrome. Further, the coexistence of CD in a patient with one autoimmune endocrinopathy may increase the risk for involvement of multiple endocrine glands. For example, a recent study suggests the risk of AIT was increased in patients with T1DM and CD (HR 1.67, 95% CI 1.32 – 2.11) compared to those with T1DM alone. The highest risk occurred in those with CD for 10 years or more (HR 2.22, 95% CI 1.49-3.23) (147).

In addition to the associations of CD with AIT, TIDM and Addison's disease, CD has rarely been described in association with idiopathic hypoparathyroidism and autoimmune hypophysitis in separate isolated reports or case series (148-152). One study suggested a potential mechanism linking hypoparathyroidism and untreated CD - cross-reactivity between CD-specific EMA antibodies and parathyroid tissue leading to parathyroid atrophy (153). This mechanism, however, has not been confirmed. Further, a more recent systematic investigation reported no increased risk of CD in patients with idiopathic hypoparathyroidism (148). The association between CD and autoimmune hypophysitis has not been well-defined to date.

Summary and Key Points

Patients with CD are at increased risk for metabolic bone disease and a number of less frequent autoimmune and non-autoimmune endocrine disorders. The patient described in the Case Report illustrates several endocrine conditions associated with CD and underscores key points evident from review of the literature on the endocrine complications of CD. Importantly, the diagnosis of CD is often delayed in those presenting with extra-intestinal manifestations rather than classic symptoms of malabsorption (1,2,7). Early diagnosis may be facilitated by adherence to published guidelines that include fatigue and weight loss alone as indications to test for CD (2).

Osteoporosis is a common finding in CD and its evaluation may lead to diagnosis of CD, as described in the Case Report. Consistent with the literature on metabolic bone disease in CD (14,19,28), the pathogenesis of bone loss in this case involved calcium (if not vitamin D) malabsorption leading to osteomalacia (presumably), compensatory secondary hyperparathyroidism, and increased bone turnover. Although all laboratory abnormalities related to the patient's metabolic bone disease resolved with duodenal mucosal healing on GFD, restoration of BMD was incomplete, as shown in numerous studies (though antiepileptic therapy may have contributed to residual reduced BMD in this case (154)). As is often the case in clinical practice, pharmacological osteoporosis treatment was ultimately needed for the patient described.

The patient's presentation and course were also marked by clinical and laboratory findings consistent with the less frequent CD complication of incomplete androgen insensitivity, with partial resolution on GFD as reported in several studies of men with CD (119-121); as with persistent osteoporosis in this case, the mild, residual elevation of SHBG on GFD may have been

attributed to treatment with phenytoin, which is known to increase circulating SHBG levels (155). Recent studies also suggest other reproductive consequences of CD, not seen in this case, including hypogonadism and preterm labor in women. The case highlights that testing for CD in those with osteoporosis or reproductive dysfunction should be considered due to the possibility of improvement after the diagnosis of CD and institution of a GFD.

Finally, the patient had evidence of CD-associated endocrine gland autoimmunity, in this case AIT (60,61) and thyroid parenchymal heterogeneity but no overt thyroid dysfunction. Strong epidemiological associations between CD and several autoimmune endocrinopathies, including not only AIT but also T1DM and Addison's disease, have been established by recent large prospective cohort studies. Common genetic variants and HLA haplotypes are thought to predispose to both CD and endocrine autoimmunity, though much of the available data is associative in nature and exact mechanisms remain unclear.

In conclusion, the endocrine complications of CD - many manifested by the patient reported herein - are not uncommon but remain incompletely understood. Research into underlying mechanisms and associations is warranted and will likely inform improvement in clinical diagnosis and treatment. Unfortunately, the diagnosis of CD in those manifesting only endocrine dysfunction may be delayed. Screening for CD may be appropriate in certain high prevalence groups such as those with osteoporosis, hypothyroidism, T1DM or multiple endocrinopathies and is recommended by some experts (156). Likewise, gastroenterologists who care for CD patients must have a high degree of suspicion for possible concomitant endocrine disorders, particularly those that are frequent, such as osteoporosis, vitamin D deficiency and hypothyroidism.

Key Points:

1) Patients with CD are at increased risk for metabolic bone disease and a number of less frequent autoimmune and non-autoimmune endocrine disorders.
2) Diagnosis of CD is often delayed in those presenting with extra-intestinal manifestations.
3) Screening for CD may be appropriate in certain high prevalence groups such as patients with osteoporosis, hypothyroidism, T1DM and multiple endocrinopathies and is recommended by some experts.
4) The link between autoimmune endocrinopathies and CD is incompletely understood but is likely due in part to HLA genotypes predisposing to both conditions.

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Declaration of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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