

Endocrinopathies in celiac disease: when the endocrinologist sees what is invisible to the gastroenterologist

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Summary. Celiac disease (CD) is a systemic, immune mediated and genetically determined small intestinal disorder characterized by intolerance to dietary gluten that generally presents with gastrointestinal symptoms in young children and extra-intestinal manifestations. Furthermore, there is close association between CD and endocrine diseases, including diabetes, autoimmune thyroid diseases, growth and pubertal disorders, etc. probably due to the presence of a common genetic predisposition. The present review aims to highlight and give more insight to the endocrine changes in CD, especially when there are few or no gastrointestinal symptoms and to emphasize on screening opportunities in some endocrine diseases. (www.actabiomedica.it)

Key words: celiac disease, endocrine disorders, autoimmune thyroiditis, diabetes, adrenal insufficiency

Introduction

Celiac disease (CD), or gluten-sensitive enteropathy is a systemic immune-mediated small intestinal disorder that occurs in genetically susceptible people after ingestion of gluten containing proteins found in wheat, rye and barley grains and recovers when gluten-containing cereals are withdrawn from the diet. Patients may present with only subtle symptoms which is the main reason why the disease is highly underdiagnosed (1). Symptomatic patients present with diarrhea, malabsorption and weight loss associated with a mucosal inflammatory process in the proximal small intestine that may extend for variable distances into more distal jejunum and ileum. Thus, the disease is generally considered to affect mainly the gastrointestinal tract (2). In recent years, it has become increasingly appreciated even without gastrointestinal symptoms- thus patients may be referred initially to specialists other than gastroenterologists- being documented in up to 2% of the serologically-studied populations where typical gastrointestinal symptoms are not obvious, and perhaps,

higher using endoscopic screening biopsies for some referred patients (3).

Anti-tissue transglutaminase and anti endomysial Antibodies are highly sensitive and specific for diagnosis of CD, but histologic studies are the gold standard for establishing the diagnosis (3, 4).

Hence, celiac disease or its complications have other extra-intestinal presentations, endocrine manifestation should be noted. Moreover, endocrinologists should consider celiac disease in any autoimmune condition. This manuscript aims to highlight and give more insight to the endocrine changes in CD, especially when there are few or no gastrointestinal symptoms and to emphasize on screening opportunities in some endocrine diseases.

Endocrinological diseases associated with celiac disease

1. *Insulin-dependent diabetes mellitus (IDDM)*

The association between celiac disease and IDDM is well recognized since long time. In the very early

reports, it was estimated that 1.0–1.5% of diabetic children suffered from celiac disease and presented with classical symptoms such as malabsorption, diarrhea and failure to thrive with poor diabetes control and frequent episodes of hypoglycemia. Diarrhea may easily have been misinterpreted as due to autonomic diabetic neuropathy or exocrine pancreatic insufficiency, and the diagnosis of celiac disease was therefore sometimes delayed or missed especially in the absence of serological screening tests (4–6). Nowadays, the frequency of celiac disease in patients with IDDM has increased to range from 3.5–7.4% in many latest studies (7–11). This increment might be explained by greater awareness, the introduction of more diagnostic serological antibody tests and also by recognition of the non-classical presentation of celiac disease as short stature, refractory anaemia, delayed puberty, osteopenia, enamel defects, and recurrent aphthous stomatitis (12).

There is evidence of common genetic basis as both diseases are associated with the major histocompatibility complex class II antigen DQ2, DQA1*501 and DQB1*201 and seven shared non-human leucocyte antigen (HLA) loci (13).

Failure to recognize co-existing CD with longer duration of untreated patients may predispose the individuals to increased risk of growth failure, osteoporosis, infertility and gastrointestinal lymphoma. Moreover, continuous exposure to gluten may facilitate development of other autoimmune diseases apart from CD (14). Therefore, it is important to actively screen for CD in patients with IDDM at the time of diagnosis and also during follow up later in life every 1–2 years as the sequence of appearance of CD in IDDM patients cannot be predicted. This will help optimize insulin therapy, achieve good glycemic control and avert the risk of complications both due to T1DM and CD (15).

The impact of a gluten-free diet on the metabolic control of diabetes may depend on the symptoms of celiac disease in diabetic patients. In malnourished patients, the treatment of newly detected celiac disease had an unequivocal positive effect as alleviation of the intestinal symptoms, evident weight gain and improved metabolic control in particular the reduction of number of severe hypoglycemic episodes (5, 8). This posi-

tive effect of a gluten-free diet is not as straightforward as it was previously, this is due to regular screening and early diagnosis making most of celiac patients in good condition and do not suffer from malabsorption at the time of diagnosis. Therefore the impact of dieting on metabolic control in patients with IDDM and celiac disease cannot be considered unanimously positive.

2. *Thyroid Diseases*

There is an association between CD and thyroid disease such as graves and Hashimoto thyroiditis near 2–7% that it means 3 folds higher compared to normal population (16).

In several studies, they have suggested different mechanisms for this association such as genetics particularly HLA haplotypes B8 and DR3 which were noted to increase frequencies of children with CD as well autoimmune thyroid disease. An alternate hypothesis is also possible that 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 (17). Another theory is the cross reaction of tissue transglutaminase IgA (TTG- IgA) with thyroid tissue (18).

The linkage between these two disorders may have important clinical implications. Hypothyroidism may make clinical recognition of CD difficult as the severity of the diarrhea or weight loss may be more limited due to increased time for intestinal transit or fluid retention due to the reductions of circulating thyroid hormone. Also, CD reduces small intestinal surface absorptive area causing failure of hypothyroid patients to respond to oral thyroid replacement therapy. In addition, an apparent failure to respond to a gluten-free diet in CD patients may be attributed to impaired absorption and increased transit rate in hyperthyroidism. Usage of gluten free diet (GFD) is in controversy; in some studies they deny protection of GFD and in others they find that using GFD can normalize thyroid function and taper thyroxine dosage with recovery of clinical or sub-clinical autoimmune thyroid disease (19, 20).

Malignant thyroid lymphomas have been recorded in CD patients, it is rare T-cell lymphoma, indicating another site of extra-nodal lymphoma that may complicate the clinical course of CD, possibly due to its shared embryological developmental links with the gastrointestinal tract (21).

Thus, it is important to do serological screening for autoimmune thyroid disease in patients with celiac disease and vice versa by rigorously searching for even subclinical autoimmune thyroid conditions in celiac disease (22).

3. Other endocrine disorders

Adrenal insufficiency may occur in CD patients. Indeed, CD may be present in association with isolated autoimmune adrenocortical failure (autoimmune Addison's disease) or in the setting of polyendocrine failure that may include Addison's disease, thyroiditis, ovarian failure and CD (23, 24).

It was recommended that cases with adrenal insufficiency should be screened for CD specially if there is failure to respond to substitute hormonal treatment and also CD patients should be investigated for adrenal insufficiency specially if associated with recurrent hypoglycemia (23, 25).

Hypoparathyroidism has been rarely recorded with CD, however in celiac patients with severe hypocalcemia or tetanic seizures this rare association should be borne in mind. In a recent report, it was noted that a gluten-free diet had a beneficial effect on calcium regulation in those with concurrent CD and hypoparathyroidism (26, 27).

Anti-pituitary antibodies were detected in 42% of newly diagnosed CD patients in an Italian study (28). Interestingly, this 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 contribute in linear growth impairment in CD. A gluten-free diet reported to result in rapid catch-up growth and normalization of pituitary function (29). Growth hormone replacement may play role in children with CD and short stature, despite a gluten-free diet over a 1 year period (30).

Other evidence of alteration of pituitary gland is increased prolactin levels in recently diagnosed CD in

pediatric patients and its levels were decreased over a few months with a gluten-free diet (31).

Menarche takes place later and menopause earlier in celiac women i.e. the fertility period is shortened. Also, ovarian failure causing infertility is recognized in females with CD. Moreover, serologically-based studies showed that over 4% of infertile females proved to have CD confirmed by subsequent biopsy. Some of these females showed later subsequent successful pregnancy after treatment with a gluten free diet (32). 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 (33).

It has long been recognized that osteomalacia, osteoporosis, bone pain, and fractures are complications of celiac disease (34). The mechanisms of disturbances in bone metabolism in celiac disease are poorly understood. The initial and probably main event is calcium malabsorption which is primarily caused by villous atrophy and secondarily by coexisting vitamin D deficiency. Impaired intestinal calcium malabsorption leads to secondary hyperparathyroidism that increases bone turnover (35, 36).

Conclusions

Celiac disease is associated with many extra intestinal manifestations including diverse endocrinological disorders with symptoms being sometimes, if not mostly, subtle or atypical. This highlight the importance of awareness and early regular screening for such complications. The detection of a monoglandular endocrinopathy in CD may only be part of an evolving and dynamic process with the appearance of other endocrinopathies at a later stage in CD.

References

1. Corazza GR, Frisoni M, Treggiari EA, Valentini RA. Sub-clinical celiac sprue. Increasing occurrence and clues to its diagnosis. *J Clin Gastroenterol* 1993; 16: 16-21.
2. Freeman HJ, Chopra A, Clandinin MT, Thomson AB. Recent advances in celiac disease. *World J Gastroenterol* 2011; 17: 2259-2272.

3. Freeman HJ. Detection of adult celiac disease with duodenal screening biopsies over a 30 year period. *Can J Gastroenterol* 2013; 27: 405-408.
4. Thain ME, Hamilton JR, Ehrlich RM. Coexistence of diabetes mellitus and celiac disease. *J Pediatr* 1974; 85: 527-529.
5. Visakorpi JK. Diabetes and coeliac disease. *Lancet* 1969; 2: 1192.
6. 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.
7. de Freitas IN, Sipahi AM, Damiao AO, de Brito T. Celiac disease in Brazilian adults. *J Clin Gastroenterol* 2002; 34: 430-434.
8. 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.
9. 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: 1429-434.
10. 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.
11. 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.
12. Rami B, Sumnik Z, Schober E, Waldhör T, Battelino T, Bratanic N, Kürti K, Lebl J, Limbert C, Madacsy L, Odink RJ, Paskova M, Soltesz G. Screening detected celiac disease in children with type 1 diabetes mellitus: Effect on the clinical course (a case control study). *J Pediatr Gastroenterol Nutr* 2005; 41: 317-321.
13. 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.
14. Goddard CJR, Gillett HR. Complications of coeliac diseases: are all patients at risk? *Postgrad Med J* 2006; 82: 705-712.
15. Kordonouri O, Klingensmith G, Knip M, Holl RW, Aanstoot HJ, Menon PS, Craig ME; International Society for Pediatric and Adolescent Diabetes. ISPAD Clinical Practice Consensus Guidelines 2014. Other complications and diabetes-associated conditions in children and adolescents. *Pediatr Diabetes* 2014; 15 (Suppl 20): 270-278.
16. Ch'ng L, Jones M K, Kingham J G C. Celiac disease and autoimmune thyroid disease. *Clin Med Res* 2007; 5: 184-192.
17. 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.
18. Naiyer J, Shah J, Hernandez L, Kim SY, Ciaccio EJ, Cheng J, Manavalan S, Bhagat G, Green PH. Tissue transglutaminase antibodies in individuals with celiac disease bind to thyroid follicles and extracellular matrix and may contribute to thyroid dysfunction. *Thyroid* 2008; 18: 1171-1178.
19. Sategna-Guidetti, 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.
20. Lerner A, Jeremias P, Matthias T. Gut-thyroid axis and celiac disease. *Endocrine Connections* 2017; 6: R52-R58.
21. Freeman HJ. T cell lymphoma of the thyroid gland in celiac disease. *Can J Gastroenterol* 2000; 14: 635-636.
22. 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.
23. Elfström P, Montgomery SM, Kämpe O, Ekblom A, Ludvigsson JF. Risk of primary adrenal insufficiency in patients with celiac disease. *J Clin Endocrinol Metab* 2007; 92: 3595-3598.
24. 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 doi: 10.7860/JCDR/2015/10755.5748.
25. 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.
26. Matsueda K, Rosenberg IH. Malabsorption with idiopathic hypoparathyroidism responding to treatment for coincident celiac sprue. *Dig Dis Sci* 1982; 27: 269-273.
27. Saha S, Saini S, Makharia GK, Datta Gupta S, Goswami R. Prevalence of coeliac disease in idiopathic hypoparathyroidism and effect of gluten free diet on calcaemic control. *Clin Endocrinol (Oxf)* 2016; 84: 578-586.
28. 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.
29. 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.
30. Giovenale D, Meazza C, Cardinale GM, Sposito M, Mstrangelo C, Messina 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.

31. Delvecchio M, Faienza MF, Lonerio 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.
32. Freeman HJ. Infertility and ovarian failure in celiac disease. *World J Obstet Gynecol* 2015; 4: 72-76.
33. 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.
34. Scotta MC, Salvatore S, Salvatoni A, De Amici M, Ghiringhelli G, Brogginini M, Nespoli L. Bone mineralization and body composition in young patients with celiac disease. *Am J Gastroenterol* 1997; 92: 1331-1334.
35. Mautalen C, Gonzalez D, Mazure R, Vazquez H, Lorenzetti MP, Maurino E, Niveloni S, Pedreira S, Smecuol E, Boerr LA, Bai JC. Effect of treatment on bone mass, mineral metabolism, and body composition in untreated celiac disease patients. *Am J Gastroenterol* 1997; 92: 313-318
36. Collin P, Kaukinen K, Välimäki M, Salmi J. Endocrinological Disorders and Celiac Disease. *Endocrine Reviews* 2002; 23: 464-483.

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