Celiac Disease

Reinaldo Alexander, Murdani Abdullah***

*Faculty of Medicine, Universitas Indonesia/Dr. Cipto Mangunkusumo General National Hospital Jakarta

**Division of Gastroenterology, Department of Internal Medicine, Faculty of Medicine, Universitas Indonesia/Dr. Cipto Mangunkusumo General National Hospital, Jakarta

Corresponding author:

Murdani Abdullah. Division of Gastroenterology, Department of Internal Medicine, Dr. Cipto Mangunkusumo General National Hospital. Jl. Diponegoro No.71 Jakarta Indonesia. Phone:+62-21-3153957; Facsimile: +62-21-3142454. E-mail: murdani08@gmail.com.

ABSTRACT

Celiac disease is a multisystem autoimmune disorder, which is induced by dietary gluten exposure. This disease usually found in European population, but with the increase of Asian population tendency to eat western style, which contain gluten, celiac disease frequency is expected to increase in Asian population for the near future. The finding of diagnostic modalities which is highly sensitive and specific, starting with the antigliadin, and then the antiendomysium and anti-transglutaminase antibodies, has increased the awareness of clinicians and patients towards this condition. The understanding of definition, pathogenesis, diagnostic procedure, and current management of celiac disease is needed to avoid morbidity and mortality of this disease.

Keywords: *Celiac disease, autoimmune disorder, dietary gluten*

ABSTRAK

Penyakit celiac adalah gangguan autoimun yang bersifat multisistem, yang dicetuskan oleh paparan terhadap gluten dalam diet. Penyakit ini dahulu banyak ditemukan pada populasi Eropa, namun seiring meningkatnya kecenderungan masyarakat Asia untuk mengadopsi pola makan dari negara barat yang banyak mengandung gluten diperkirakan kejadian penyakit ini akan meningkat pada populasi Asia ke depannya. Munculnya modalitas pemeriksaan yang sangat sensitif dan spesifik, mulai awalnya dari ditemukannya antigliadin, dan kemudian antiendomysium dan antibody anti-transglutaminase telah meningkatkan kepedulian klinisi dan juga para pasien akan penyakit ini. Pemahaman akan definisi, patogenesis, cara diagnosis dan penanganan terkini dari penyakit ini perlu dipahami oleh para dokter agar dapat menghindari morbiditas dan mortalitas yang terkait dengan penyakit ini.

Kata kunci: *penyakit celiac, penyakit autoimun, diet gluten*

INTRODUCTION

Celiac disease (CD) is a multisystem autoimmune disorder precipitated by exposure to dietary gluten in genetically predisposed individuals.[1–8] In the past, this condition was considered a rare disorder, mostly affecting individuals of European origin, with onset during the first years of life. After the emergence of highly sensitive and specific serological tools, studies have shown that CD is one of the commonest, lifelong disorders affecting mankind all over the world. Many developing countries in Asia including Indonesia are likely to have increasing incident of celiac disease in the near future given the diffuse tendency to adopt Western, gluten-rich dietary patterns.[4]

The diagnosis of CD can be challenging because the clinical spectrum of the disease varies, and some

individuals present with mild symptoms. Many new diagnoses now are made from screening high risk individuals. The common feature among these at-risk groups is that they carry the alleles encoding HLA-DQ2 or HLA-DQ8.[7] CD causes enteropathy of the small intestine, resulting in poor absorption of nutrients leading to malabsorption with its own concequences.[1,2,5,7,9]

This disease contribute substantially to childhood morbidity and mortality in many developing countries, hence a timely diagnosis and give the best management to avoid morbidity and mortality of this disease.

DEFINITION

Gluten can be defined as the rubbery protein mass that remains when wheat dough is washed to remove starch. The major protein components of gluten, gliadins and glutenins, are storage proteins in wheat. Gluten and gluten-related proteins are present in wheat, rye, and barley, and are used widely in food processing to give dough the desired baking properties, add flavors, and improve texture.[5,9] Celiac disease (CD) is a chronic, multiple-organ autoimmune disease that affects the small intestine in genetically predisposed children and adults. It is precipitated by the ingestion of gluten-containing food. It may also be referred to as celiac sprue, gluten-sensitive enteropathy, or nontropical sprue.[1–8]

EPIDEMIOLOGY

Early epidemiological studies regarded celiac disease as a disease of individuals of Caucasian ancestry, located mainly in Europe and North America. However, further studies in other areas of the world revealed a similar prevalence of celiac disease there. The prevalence of the disorder is globally 1%, but wide variations between countries have been shown.[5] Meta-analysis conducted by Singh et al. found that CD is not uncommon in Asia and the sero-prevalence and prevalence of CD in Asia is 1.6% and 0.5%, respectively.[6] Children with type 1 diabetes, Down's syndrome, autoimmune thyroid disease, Turner syndrome, William's syndrome, IgA deficiency, autoimmune liver disease, and have first degree relatives with CD has increased prevalence in developing this disease.[2]

GENETICS AND PATHOGENESIS OF CELIAC DISEASE (CD)

Celiac disease is characterized by inflammatory-mediated atrophy of the villi that protrude from the mucosa of the small intestine. The major environmental antigen associated with CD is gliadin, a protein found in wheat. The genetic predisposition is linked to the presence of certain class II HLA alleles, specifically HLA-DQ2 and HLA-DQ8.[5,8,9] Wheat gluten is composed of gliadins and glutenins. The α-gliadin proteins have some unique characteristics, including large numbers of proline and glutamine residues. The prolines limit proteolytic degradation, resulting in the presentation of large, immunogenic peptides. The glutamine residues in gliadin are excellent substrates for the enzyme tissue transglutaminase (TTG). TTG deamidates select glutamines to glutamates, increasing the antigenicity of the peptides. The deamidated gliadin peptides demonstrate a high-affinity interaction with the peptide binding groove of the HLA-DQ2 and HLA-DQ8 molecules. The HLA/deamidated gliadin peptide complex then interacts with T-cell receptors (TCRs), activating gliadin-specific CD4 T cells. These T cells subsequently interact with B cells, initiating production of antibodies specific for deamidated gliadin. Activated $CD4^+$ T cells is secreting mainly Th1 cytokines such as IFN-γ, which induces the release and activation of MMPs by myofibroblasts, finally resulting in mucosal remodeling and villus atrophy. Additionally, Th2 cytokines are produced driving the production of (auto-) antibodies to gluten and TG2. Other cytokines such as IL-18, IFN-α, or IL-21 seem to play a role in polarizing and maintaining the Th1 response. Furthermore, IL-15 links the adaptive immune system to innate immune responses. The schematic processes of immunological interaction in celiac disease can be seen in figure 1 and 2.[10]

Upon stimulation with gliadin peptide p31-49 (and other peptides), epithelial cells, macrophages, and dendritic cells secrete IL-15, which in turn up-regulates both the NKG2D receptor on IELs and its epithelial ligand MICA. The thus stimulated cytotoxic lymphocytes induce increased epithelial apoptosis and permeability. Furthermore, the NKG2C receptor on a subset of natural killer–like IELs is stimulated by its epithelial ligand HLA-E on epithelial cells, resulting in their proliferation and cytotoxicity, whereas stimulation of $\gamma\delta^+$ $CD8^+$ IELs bearing the NKG2A receptor via HLA-E induces TGF-β secretion and therefore a regulatory phenotype. Gliadin (cereal) peptides can also directly elicit innate immune responses in macrophages and dendritic cells via pattern recognition receptors such as Toll-like receptor 4 or other MyD88-dependent pathways. This drives maturation of these cells and secretion of inflammatory

cytokines such as IL-1β , IL-8, tumor necrosis factor α, and MCP-1, which can potentiate the adaptive immune response to gluten. APC, antigen presenting cell; pDC, plasmacytoid dendritic cell.[10]

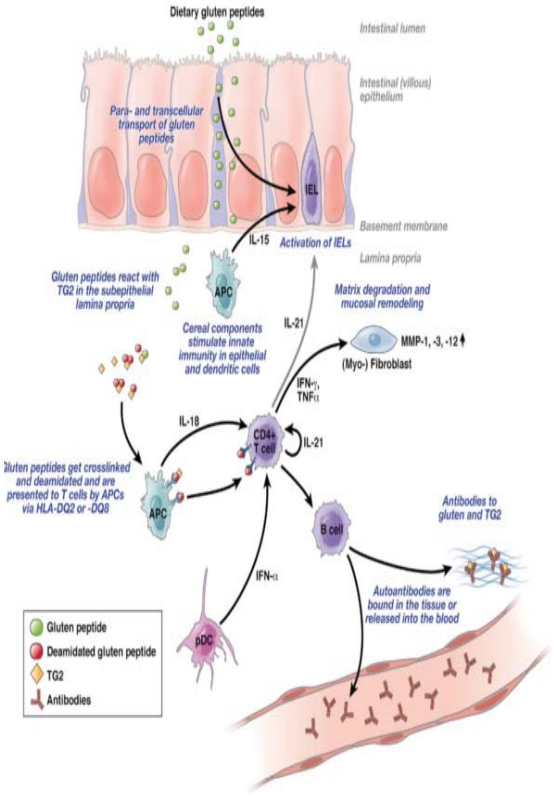

Figure 1. Pathogenesis of celiac disease. Gluten peptides that are highly resistant to intestinal proteases reach the lamina propria, via either epithelial transcytosis or an increased epithelial tight junctional permeability. Cross-linking and particularly deamidation of gluten peptides by TG2 creates potent immunostimulatory epitopes that are presented via HLA-DQ2 or HLA-DQ8 on antigen-presenting cells.[10]

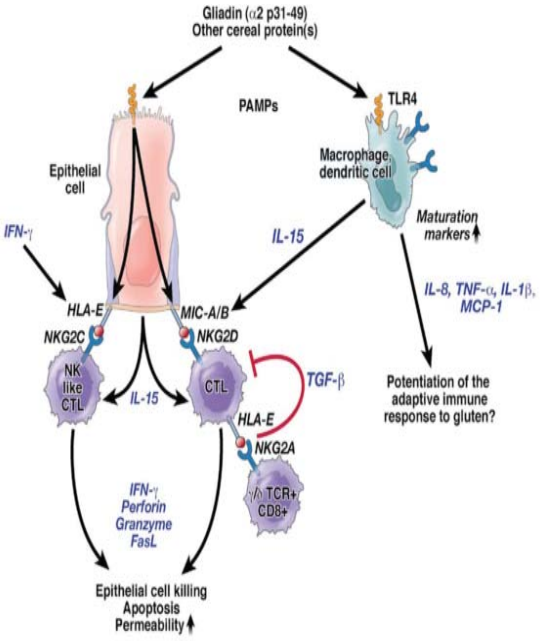

Figure 2. Innate immune responses in celiac disease

SCREENING OF CELIAC DISEASE (CD)

The most important reason for the relatively low rate of CD diagnosis is failure to consider testing. CD is often not considered due to its wide range of clinical presentation. CD diagnosis rate is increasing due to both increased true prevalence and improved awareness of its variable clinical presentation. Recommendations are now available to help clinicians decide which patients should be tested for CD (Table 1).[8]

Table 1. Who should be tested for celiac disease[8]

High Risk Patients Routinely Test for CD: Consider Endoscopy even if Serology negative	Medium Risk Patients Consider CD Serologic Testing: CD Sufficiently Excluded if Serology negative	Low Risk Patients Consider testing if refractory to standard therapy or other clinically unusual features: CD sufficiently excluded if serology negative.
(1) Chronic gastrointestinal symptoms with a family history of celiac disease or a personal history of autoimmune disease or IgA deficiency (2) Biopsy proven dermatitis herpetiformis (3) Chronic diarrhea (4) Failure to thrive in children (5) Iron deficiency anemia refractory to oral supplementation	(1) Irritable bowel syndrome (2) Elevated liver function tests (3) Iron deficiency anemia (4) Fatigue/lethargy (5) Chronic gastrointestinal symptoms without a family history of celiac disease or a personal history of autoimmune disease (6) Peripheral neuropathy (7) Ataxia (8) Dental enamel defects (9) Recurrent aphthous ulcerations (10) Hyposplenism (11) Fertility abnormalities (12) Down's or Turner's syndrome (13) Known IgA deficiency (14) Microscopic colitis	(1) Osteopenia/osteoporosis (2) Fibromyalgia (3) Chronic Fatigue Syndrome (4) Heartburn/GERD (5) Acute or chronic pancreatitis (6) Alopecia (7) Myalgias/Arthralgias (8) Autoimmune liver disease (9) Personal history of autoimmune disease or connective tissue disease without ongoing unexplained symptoms (10) Skin lesions other than dermatitis herpetiformis (11) Headaches including migraines (12) Mood disorders (13) Attention deficit disorder/cognitive impairment (14) Epilepsy (15)Restless leg syndrome

Table 2. Patients who might require testing for Celiac Disease.[7]

Symptoms and Signs		Associated conditions
Gastrointestinal	**Extraintestinal**	
	Iron-deficiency anemia	
	Other deficiency states (vitamin B12, vitamin D, folate,	
Chronic diarrhea	zinc, vitamin B6)	Family history of celiac disease
Chronic abdominal pain	Fatigue	Type 1 diabetes
Malabsorption	Recurrent aphthous stomatitis	Autoimmune thyroid disease
Bloating	Increased hepatic transaminase levels	Autoimmune liver disease
Erratic bowel habit (similar to IBS)	Short stature	Selective IgA deficiency
Constipation (more commonly in children)	Delayed puberty/menarche Amenorrhea	Sjögren syndrome
Failure to thrive/weight loss	Early menopause	Down syndrome
Anorexia	Dermatitis herpetiformis	Turner syndrome
Vomiting	Osteopenia/osteoporosis	Williams syndrome
GERD	Dental enamel hypoplasia	
	Peripheral neuropathy	
	Hyposplenism	

DIAGNOSIS STRATEGIES IN CELIAC DISEASE

The clinical manifestations of celiac disease are classic (signs and symptoms of malabsorption including diarrhea, steatorrhea, weight loss, or growth failure), nonclassic and symptomatic (with evident gastrointestinal and/or extra-intestinal symptoms), or asymptomatic.[5,7,9] Kelly, et al summarized presents information about individuals who may be at increased risk for celiac disease and for whom the threshold for testing is, accordingly, lower. This can be seen in table 2.[7]

Four guidelines on CD diagnosis have been published by gastrointestinal organizations since 2012. All guidelines include the combined use of biopsy and serologic analyses for diagnosis. According to American College of Gastroenterology (ACG) 2013 CD guidelines combination of both small intestinal biopsy and serologic tests (anti-tissue transglutaminase (tTG) or anti-deamidated gliadin peptide (DGP) are recommended for diagnosis of CD.[11] A consensus guideline in 2016 by the European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) proposed a non-invasive method of diagnosing CD in select pediatric patients. The ESPGHAN algorithm suggested that, in pediatric

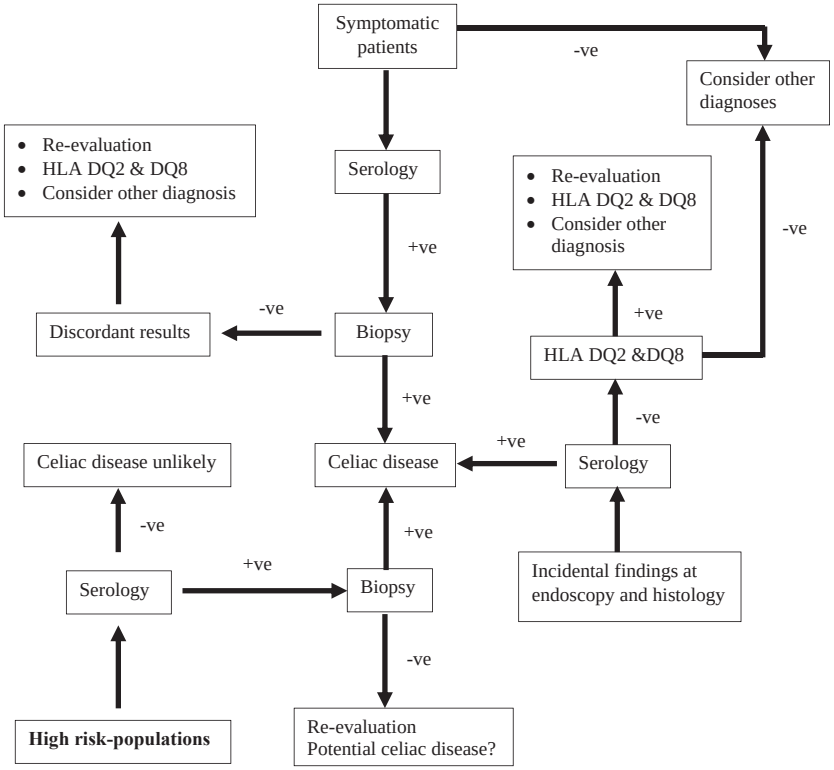

Figure 3. Approach to celiac disease diagnosis (confirm if biopsy is positive)[7]

patients who have symptoms consistent with CD can be diagnosed without biopsy confirmation if they have an IgA tTG titer >10-fold above the upper limit of normal, a positive endomysial antibody (EMA) in a separate blood sample, and carry the HLA DQ2 or DQ8 haplotype.[2] The British Society of Gastroenterology recommendations for adult CD diagnosis suggest that serologic tests, either tTG, EMA, or DGP should be done as the first step in diagnosis, followed by small intestinal biopsy is a definitive test to diagnose CD.[12] Meanwhile, recent guidelines for adult CD patients from the World Gastroenterological Association recommend serologic tests including anti-tTG and/or anti-EMA, or anti-DGP for diagnosis and biopsy suggested but not considered mandatory for CD diagnosis which is appropriate for countries with limited healthcare resources.[5] The guidelines overlap substantially with the major difference between all four guidelines being that ACG and BSG mandates intestinal biopsy to confirm the diagnosis of CD, while ESPGHAN and WGO allow diagnosis of CD without biopsy in certain conditions. Figure 3 showed an integrated approach to celiac disease diagnosis.[7]

Endoscopy and Histology

We should suspect that a person has CD if the endoscopy finds scalloping of duodenal folds, fissuring over the folds and a mosaic pattern in the mucosa, flattening of the folds, decreasing number of folds with maximum insufflation, absence of villi at magnification, and granular appearance of the duodenal bulb. An example of classical scalloping of duodenal mucosa seen in Celiac disease at endoscopy can be seen in figure 4.[8] Intestinal mucosal biopsies should always be obtained when any of the above endoscopic features are observed. Nevertheless, endoscopic biopsies should also be obtained even if the endoscopic folds appear normal, but there is a clinical suspicion of the disease, since many patients with celiac disease may have apparently normal folds. An absence of endoscopic findings has a low predictive value for discarding the possibility of celiac disease in low-risk populations.[5]

A combination of villous abnormalities seen at intestinal biopsies, together with a positive serological test, is the gold standard diagnostic criterion for celiac disease. A modified Marsh classification for villous abnormalities is now widely used for assessing the severity of villous atrophy in clinical practice. While the histological changes seen in celiac disease are considered to be characteristic, they are not pathognomonic, as similar changes can be seen in several other conditions, including tropical sprue, parasitic infection, common variable immunodeficiency, human immunodeficiency virus (HIV) enteropathy, and drug and enteropathy induced by food allergy (such as to cow's milk). Four to six biopsy samples must be taken from the second part of the duodenum, and from the duodenal bulb. In patients with ultrashort celiac disease, pathology may be confined to the duodenal bulb — highlighting the importance of taking biopsies from that area. Biopsies must be taken when patients are on a gluten-containing diet (at least 3 g of gluten/day for 2 weeks).

Under light microscopy, the most characteristic histological findings in patients with celiac disease who are taking a gluten-containing diet includes increased density of intraepithelial lymphocytes (> 25/100 epithelial cells), crypt hyperplasia, with a decreased villi/crypt ratio, blunted or atrophic villi, mononuclear cell infiltration into the lamina propria, or epithelial changes, including structural abnormalities in epithelial cells.[5]

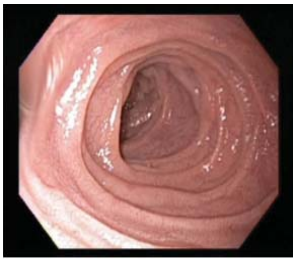

Figure 4. Classical scalloping of duodenal mucosa seen in Celiac disease at endoscopy[8]

Table 3. Modified Marsh classification of gluten-induced small-intestinal damage.[5]

Stage	Description
Stage 0	Pre-infiltrative mucosa; up to 30% of patients with dermatitis herpetiformis (DH) or gluten ataxia have small-intestinal biopsy specimens that appear normal.
Stage 1	Increase in the number of intraepithelial lymphocytes (IELs) to more than 25 per 100 enterocytes with a normal crypt/villi ratio.
Stage 2	Crypt hyperplasia. In addition to the increased IELs, there is an increase in crypt depth without a reduction in villus height
Stage 3	Villous effacement. This is the classic celiac disease lesion. It is found in 40% of DH patients. Despite marked mucosal changes, many individuals are asymptomatic and are therefore classified as having subclinical or silent celiac disease. This lesion is characteristic, but not pathognomonic, of celiac disease and can also be seen with severe giardiasis, infantile food allergy, or post-enteritis syndrome, graft-versus-host disease, chronic ischemia of the small intestine, tropical sprue, immunoglobulin deficiencies, and other immune deficiencies and allograft rejection.

TREATMENT

The only treatment for celiac disease, at present, is a strictly gluten-free diet for life. No foods or medications containing gluten from wheat, rye, or barley or their derivatives can be taken, as even small quantities of gluten may be harmful. The safe limit of gluten intake varies from patient to patient and has been considered to be 10–100 mg/day, although a subsequent study indicated that the upper limit should be no more than 50 mg/day. Approximately 70% of patients report an improvement in symptoms within 2 weeks of starting the gluten-free diet.[5,7,10–12]

NON-RESPONSIVE AND REFRACTORY CELIAC DISEASE

Non-responsive celiac disease (NRCD) can be defined as persistent or recurrent symptoms, signs, or laboratory findings consistent with active celiac disease, despite at least 12 months of treatment with the GFD.[7] Meanwhile, refractory celiac disease (RCD) can be defined as persistent or recurrent small-intestinal villous atrophy with symptoms of malabsorption, despite 12 months or more of a strict GFD, in the absence of an overt lymphoma or another condition that causes villous atrophy. RCD is characterized by the absence (type I) or presence (type II) of an aberrant population of IELs that lack lineage differentiation surface markers (eg, CD4, CD8, or the interleukin-2 receptor) but are positive for cytoplasmic CD3, indicating a T-cell phenotype. The prognoses for patients with RCD I and for RCD II differ markedly. RCD I is associated with severe symptoms and malabsorption, but life expectancy is not greatly reduced; the disease often responds to treatment with topical steroids and enteric delivery of budesonide.[5,7,13]

COMPLICATION AND PROGNOSIS

Patients with (long-term untreated) celiac disease have an elevated risk for benign and malignant complications, and mortality. Cancer development has the highest risk in the initial years after diagnosis. Malignancy as complication of CD including malignant lymphomas, small-bowel adenocarcinoma, oropharyngeal tumors. Non-malignancy complication includes unexplained infertility, impaired bone health and growth (osteoporosis), bone fractures, and adverse pregnancy outcome.[5]

There are several meta-analysis concerning the risk of developing thyroid disease, kidney disease, venous thromboembolism, and obstetric complications in patients with celiac disease. Sun, et al, in their meta-analysis concluded that the prevalence of thyroid disease, especially euthyroidism autoimmune thyroid disease and hypothyroidism, in patients with CD is increased compared with that in controls, which suggests that CD patients should be screened for thyroid disease.[14] Meanwhile, in meta-analysis conducted by Wijarnpreecha et al, demonstrated an increased risk of kidney diseases including diabetic nephropathy and IgA nephropathy among patients with CD.[15] Venous thromboembolism also increased in patients with CD. Chronic inflammation which leads to hypercoagulable state and also vitamin deficiencies related to malnutrition has been postulated as the cause of this complication in meta-analysis conducted by Ungprasert et al.[16] Finally, a meta-analysis conducted by Saccone et al, conclude that women with celiac disease had a significantly higher risk of developing obstetric complications including preterm birth, intrauterine growth restriction, stillbirth, low birth weight and small for gestational age.[17]

MONITORING

Celiac disease is a lifelong inflammatory condition that affects multiple organ systems, so patients should be followed up routinely. There are no differences in recommendations for monitoring symptomatic vs. asymptomatic patients. Based on expert consensus, at the time of diagnosis, patients should be evaluated for common co-existing autoimmune conditions, such as thyroid and liver diseases, as well as deficiencies in iron, vitamin D, and vitamin B12. There is general agreement among guidelines (Table 5) that patients should be examined at least twice in their first year after diagnosis to monitor symptoms, dietary adherence, nutrition, body mass index, and serologic features.[7]

CONCLUSION

Celiac disease is a multisystem autoimmune disorder triggered by exposure to dietary gluten in genetically predisposed individuals and still pose as a problem for clinician. It is still one of the commonest, lifelong disorders affecting mankind all over the world. Chronic inflammation causes enteropathy in CD and associated with poor absorption of nutrients leading to malabsorption and an increase in morbidity and mortality. If not treated well, this condition can elevate risk for benign and malignant complication especially cancer, lymphomas, and other complication such as thyroid disease, kidney disease, venous thromboembolism, and obstetric problem. Diagnosis

Table 5. Monitoring in Celiac Disease.[7]

Test	Interval	Comments
Clinical evaluation	Annually or if recurrent symptoms	Normal titers are insensitive for ongoing gluten exposure or enteropathy
Serology	Every 3–6 months until normal, then every 1–2 years	Persistently increased or increasing titers indicate significant gluten exposure
Nutritional evaluation	Every 3–6 months until normal, then every 1–2 years	Common deficiencies in iron, 25-OH vitamin D, vitamin B12, folate, and zinc Monitor for weight gain, low fiber intake, and constipation
Bone density	Once within first 2 years	Significant increases in bone density often are observed in the first year after diagnosis, many experts therefore advocate testing for the first time after 1 year on the GFD
Liver transaminases levels	At diagnosis, then every 1–2 years	Increased levels of AST and ALT are a common manifestation of celiac disease; Persistent increases or increasing levels indicate a comorbid liver disorder
Thyroid function tests	At diagnosis, then every 1–2 years	Autoimmune thyroid disease is the most common comorbid autoimmune disorder, found in approximately 15–20% of adults with celiac disease
Duodenal biopsy	Consider 1–2 years after diagnosis	Repeated biopsies, to evaluate healing, frequently are performed; however, it is not clear if this is necessary for patients with well-treated, clinically responsive celiac disease
Cancer screening	As for general population	Although rates of certain cancers are increased, these are not sufficiently common to warrant disease-specific screening

of celiac disease consist of serology examination which includes anti-TG2 and EMA, genetic testing for HLA DQ2/DQ8, endoscopy and biopsy of the small bowel mucosa. The only treatment for celiac disease is a strict lifelong gluten-free diet. For nonresponsive or refractory disease topical steroid and enteric delivery of budesonide can be considered. Patients should be examined at least twice in their first year after diagnosis to monitor symptoms, dietary adherence, nutrition, body mass index, and serologic features. Afterwards, routine follow up is needed to monitor adherence, and to detect complications due to this condition.

REFERENCES

1. Maglione MA, Okunogbe A, Ewing B, Grant S, Newberry SJ, Motala A, et al. Diagnosis of celiac disease. Agency for Healthcare Research and Quality [serial online] 2016 [cited 2017 Jun 23] Comparative Effectiveness Review No. 162. Available from: http://www.effectivehealthcare.ahrq.gov/reports/final.cfm.
2. Husby S, Koletzko S, Korponay-szabo IR. European Society for Pediatric Gastroenterology, Hepatology, and Nutrition Guidelines for the Diagnosis of Coeliac Disease. JPGN 2012;54:136–60.
3. Chou R, Bougatsos C, Blazina I, Mackey K, Grusing S, Selph S. Screening for celiac disease: evidence report and systematic review for the US Preventive Services Task Force. JAMA 2017;317:1258–68.
4. Catassi C, Lionetti E. World Perspective and Celiac Disease Epidemiology. Dig Dis Sci 2015;33:141–6.
5. Bai JC, Ciacci C, Roberto G, Fried M, Olano C, Rostami-Nejad M, et al. Celiac Disease. WGO Glob Guidel 2016;July:1–35.
6. Singh P, Arora S, Singh A, Strand TA, Makharia GK. Prevalence of celiac disease in Asia : A systematic review and. J Gastroenterol Hepatol 2016;31:1095–101.
7. Kelly CP, Bai JC, Liu E, Leffle DA. Advances in Diagnosis and Management of Celiac Disease. Gastroenterology 2015;148:1175-86.
8. Kaswala DH, Veeraraghavan G, Kelly CP, Leffler DA. Celiac Disease: Diagnostic Standards and Dilemmas. Diseases 2015;3:86-101.
9. Snyder MR, Murray JA. Celiac Disease : Advances in Diagnosis. Expert Rev Clin Immunol 2016;December:1-40.
10. Schuppan D, Junker Y, Barisani D. Celiac disease: from pathogenesis to Novel therapies. Gastroenterology 2009;137:1912–33.
11. Rubio-Tapia A, Hill I., Kelly C., Calderwood A., Murray JA. ACG clinical guidelines: Diagnosis and management of celiac disease. Am J Gastroenterol 2013;108:656-76.
12. Ludvigsson J, Bai J, Biagi F, Card T, Ciacci C, Ciclitira P, et al. Diagnosis and management of adult coeliac disease: Guidelines from the British Society of Gastroenterology. Gut 2014;63:1210–28.
13. Rowinski SA, Christensen E. Epidemiologic and therapeutic aspects of refractory coeliac disease – a systematic review. Dan Med J 2016;63:1–6.
14. Sun X, Lu L, Yang R, Li Y, Shan L, Wang Y. Increased incidence of thyroid disease in patients with celiac disease : a systematic review and meta-analysis. PLoS One 2016;11:1–13.
15. Wijarnpreecha K, Thongprayoon C, Panjawatanan P, Thamcharoen N, Pachariyanon P, Nakkala K, et al. Celiac disease and the risk of kidney diseases: a systematic review and meta-analysis. Dig Liver Dis 2016, forthcoming.
16. Ungprasert P, Wijarnpreecha K, Tanratana P. Risk of venous Thromboembolism in patients with celiac disease : a systematic review and meta-analysis. J Gastroenterol Hepatol 2016;31:1240-5.
17. Saccone G, Berghella V, Sarno L, Maruotti GM, Cetin I, Greco L, et al. Celiac disease and obstetric complications: a systematic review and meta-analysis. Am J Obstet Gynecol 2016;214:225-34.