

# Complications of Celiac Disease

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## Abstract

Celiac disease is a small bowel disorder, due to defect in gluten diet, leading to mucosal inflammation, villous atrophy and crypt hyperplasia. For the diagnosis of celiac disease, one has to be on gluten free diet. Due to commonly available various serologic tests and histopathology, celiac disease, can be categorized as asymptomatic, silent or potential. Between 80 and 90% of all patients with celiac disease remained undiagnosed. Because of this late diagnosis, patients may develop various complications including anemia, bone loss, depression and cancers. Patients may have different types of anemia including iron deficiency, folic acid or B12 deficiency. Any of these may occurred separately or may be manifested together. The same variation is seen in bone loss, starting from osteopenia, osteomalacia to osteoporosis and even dysplasias. Patient may develop lymphoma, gastric or oesophageal carcinomas as well. Celiac disease is also associated with other autoimmune illnesses as it is an autoimmune process by itself. The complications of celiac disease, is either due to direct consequence of celiac, or due to significant damage to the small intestine. With the early detection and diagnosis, the symptomatology and complications of celiac disease can be spared.

**Keywords:** complications, anemia, bone loss, cancers

## 1. Introduction

Celiac disease (CD) is one of the commonest malabsorptive syndromes, of either one or more nutrients. It was historically known as a disease of whites, but in recent era, it is as commonly seen in other parts of the world, including Asian and African countries [1, 2]. Because of its various categories starting from full blown CD, to completely asymptomatic variety, the clinical presentation dispersed among individuals. Although the commonest presentation is the gastrointestinal manifestation but many individuals may present with malignancies associated with CD. The logical answer for this diverse and late manifestation may be due to prolonged breast feeding and late commencement of gluten diet among infants, which was the usual presenting age among infants [3]. The usual age of presentation of CD now is 10–40 years [4].

In recent days, young patients still presenting with classical symptoms of CD, i.e. gastrointestinal, although may have complications at the time of initial presentation. The older individuals usually present with complications of different varieties, which make CD to diagnose late [5] (**Table 1**).

Among different categories of CD, including classical CD, atypical CD, asymptomatic and latent CD the presentation are different and thus complications.

Classical celiac disease: The classical one, including three features: villous atrophy, symptoms of malabsorption and resolution of symptoms with gluten free diet.

<b>Gastrointestinal complications</b>	<b>Non-gastrointestinal complications</b>
Malabsorption	Nutrient and mineral deficiencies
Intestinal lymphomas	Osteoporosis/osteomalacia
Collagenous sprue	Dental defects
Other GI malignancies	Idiopathic pulmonary hemosiderosis
	Glomerular IgA nephropathy
	Infertility
	Cardiomyopathy/myocarditis

**Table 1.**  
*Complications of celiac disease.*

This variant presents with malabsorption with vitamin and nutrient deficiencies. The malabsorptive symptoms include steatorrhea, weight loss, abdominal pain and diarrhea [6]. These patients also developed muscle weakness, muscle and bone pain, tooth enamel defect and lactase malabsorption [7]. These patients have various kind of nutrient and mineral deficiency including iron, folic acid, vitamin B12, vitamin D and zinc mostly, although they may have deficiency of other minerals as well.

**Non-classical and atypical CD:** The non-classical CD patients may have both gastrointestinal symptoms as in classical one, or they present with other associated manifestations of CD, including dermatitis herpetiformis, IgA deficiency, type 1 diabetes mellitus, autoimmune thyroid illness, enamel defects and infertility. These patients also have severe mucosal damage and having specific celiac antibody pattern.

**The asymptomatic or silent CD:** This variant remained undiagnosed, or incidentally diagnosed upon screening. They usually do not have any symptomatology except a little fatigue, which occurs after introduction of gluten free diet. Although these patients have classical architectural remodeling of intestinal mucosa as in classical CD, i.e. crypt hyperplasia and villous atrophy, but do not developed gastric symptoms; neither had they developed complications related to CD.

**Latent CD:** There are some patients among CD who have minor or no symptoms with normal jejunal mucosa, and remained asymptomatic if on gluten free diet. In this variant only 20% remained asymptomatic till adulthood and do not develop any complication of CD and having normal architecture throughout. The rest of the patients developed various degree of villous atrophy [8] and thus may develop complications related to CD. These patients may develop malabsorption with multiple nutrient deficiencies and lymphoma.

**Refractory CD:** It is defined as persistent or recurrent symptoms typically diarrhea and weight loss with signs of malabsorption .despite on strict gluten free diet. It is accompanied by villous atrophy. Both the variants of refractory CD is associated with increased risk of lymphoma [9].

## **2. Gastrointestinal complications of CD**

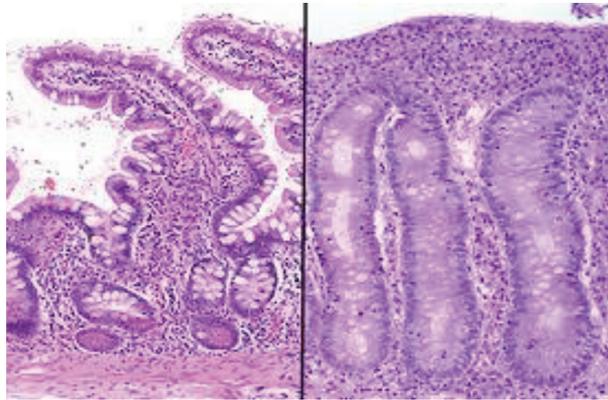
The classical CD may present with complications related to gastrointestinal symptomatology including recurrent foul smelling, bulky loose stools, and due to steatorrhea and flatulence. The mechanism of developing steatorrhea is primarily due to changes in jejunal mucosal function. Due to changes in jejunal brush border enzymatic function; these patients may develop secondary lactase deficiency, leading to diarrhea even after ingestion of milk and milk products, which further

increases the development of complications [10]. In cases of extensive involvement of ileum, patients with CD may complicate with bile acid malabsorption resulting in bile acid induced fluid secretin in the colon. Crypt hyperplasia may lead to endogenous fluid secretion (**Figures 1 and 2**).

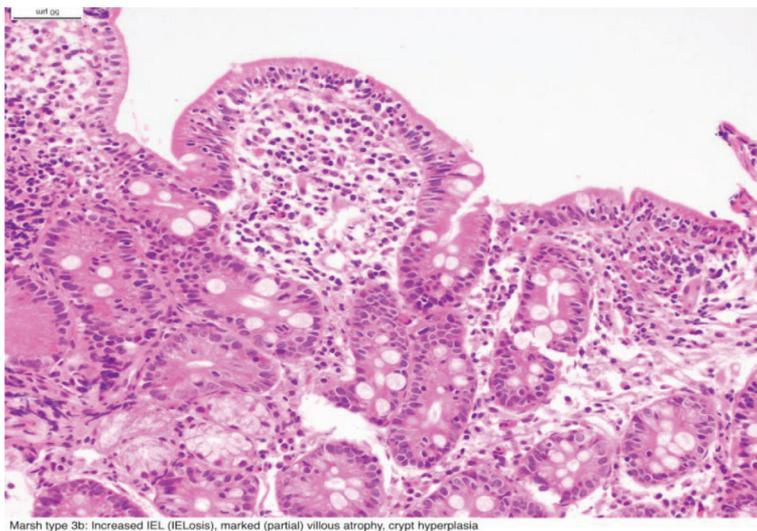
CD presenting in early age may complicate with short stature or stunted growth due to deficiency of multiple nutrients and minerals. These patients may also have severe weight loss, anemia of different types, and osteopenia. Due to shifting of classical symptoms to asymptomatic variety, patients with CD, may presents with irritable bowel syndrome type symptoms.

An association of CD is seen with gastroesophageal reflux disease, and it is much higher in CD than controls. These patients usually responded on gluten free diet within 3 months' time [11]. Eosinophilic esophagitis is another common complication among patients with CD. Patients with persistent reflux or dysphagia should be evaluated for CD [12].

Because same pro-inflammatory polymorphism of the IL-23, receptor in both ulcerative colitis and CD, they may co-exist. The incidence of ulcerative colitis is



**Figure 1.**  
*Comparison of blunting and flattening of villi with normal mucosa (left) in CD.*



Marsh type 3b: Increased IEL (IELosis), marked (partial) villous atrophy, crypt hyperplasia

**Figure 2.**  
*Villous atrophy in CD.*

much higher than Crohn's disease in patients with CD [13]. Patients having both CD and ulcerative colitis have more chances to have pancolitis as compared to patients having ulcerative colitis alone [14].

Oral lesions including erythema or atrophy, and soreness or burning sensation of the tongue have been associated with CD and can be resolved with gluten free diet.

Adult patients may rarely develop celiac crisis, presenting as profuse diarrhea and severe metabolic disturbances, if remained undiagnosed [15].

### **3. Nutrient deficiencies in CD**

Now a days, many patients with CD, may presents with no or minor gastrointestinal symptoms. The anemia including microcytic due to iron deficiency, macrocytic either due to vitamin B12 or folic acid deficiencies or even normocytic due to combined deficiencies is the initial manifestation of CD [16]. The possible explanation for high prevalence of nutritional deficiencies among CD patients include insufficient nutritional intake.

One of the commonest complications of CD is iron deficiency anemia; these patients may remain undiagnosed till their adult life [17]. The major cause of iron deficiency anemia includes decreased dietary intake, reduced absorption and blood loss. Among these causes, blood loss remained the most important one and it can be due to various sites including abdomen or urogenital. Reduced absorption of iron is an uncommon cause of iron deficiency, especially in healthy individuals and in resource rich countries. Iron is absorbed in the upper GI tract, and the duodenum is the site of maximum absorption [18]. There are multiple medical conditions which may lead to reduced absorption, and among them celiac is not an uncommon cause. The other conditions are atrophic gastritis, helicobacter pylori infection and bariatric surgery. Normal heme iron and normal gastric environment without acid reducing medications, facilitates absorption [19]. CD can contribute to anemia by several mechanisms, including iron deficiency by reduced absorption of supplemental iron and malabsorption of the other nutrients required for RBC production including B12, folic acid and copper [20]. There may also be a component of anemia of chronic disease and blood loss. Although the exact cause of blood loss in CD is unclear [21]. The causative pathology among these patients either includes mucosal abnormalities leading to oesophagitis and gastritis, or occult gastrointestinal bleeding [22]. The occult bleeding is due to excessive loss of intestinal cells and/or malabsorption of peroxidase-containing foods rather than loss of red blood cells [23]. Although the occult bleeding is not a common manifestation among patients with CD, thus occult bleeding is not a major contributing factor to iron deficiency anemia [24]. The classical presentation among these patients is recurrent iron deficiency with no recovery on supplemental therapy. The presentation of iron deficiency among these patients may include mild iron deficiency to severe heart failure.

The water soluble vitamins are B6 and folic acid which absorbed proximally and B12 which absorbed distally are the other commonly deficient vitamins [25]. The fat soluble vitamin A and D are also deficient in CD. Among these water and fat soluble vitamins, folic acid is the deficient most varying from 18 to 90% [26], followed by B12, vitamin A and D respectively. Overall vitamin deficiencies are barely seen in healthy individuals except for vitamin B12 which is commonly seen in healthy individuals [27]. The clinical presentation of folic acid includes mild cheilitis and sore mouth. Vitamin B12 and B6 deficient patients although presents with more severe manifestation including neurological symptoms.

There is deficiency of other minerals including magnesium, copper, and zinc. Minerals form only 5% of the typical human diet but are essential for normal health and function. Although magnesium deficiency in humans is very unusual, it has been seen in individuals on a highly restricted diet or with celiac disease [28]. Magnesium is absorbed throughout the small intestine but the co-efficient is very low, possibly as low as 5% [29]. Its absorption decreases following high dietary intake or when total body magnesium is sufficient [30]. Due to deficiency patients may develop scaly dermatitis and dyslipidemia. Copper is the other mineral which may reduce in CD. It is absorbed in the proximal small intestine and stomach [31]. Though rare, acquired copper deficiency has been seen in humans. The common causes include fore gut surgery, premature infants, chronic malabsorptive conditions including CD and hemodialysis [32–34]. Copper deficiency may present with fragile, abnormally-formed hairs, depigmentation of skin, muscle weakness and neurological abnormalities [35]. The neurological abnormalities are same as B12 deficiency. It may also cause anemia mimicking iron deficiency and neutropenia [36]. The other commonest deficient mineral is zinc. It is mainly absorbed in the duodenum and jejunum, and to a lesser extent in the ileum and large intestine [37]. In CD, the zinc deficiency may be due to increased endogenous losses of zinc, rather than abnormal zinc absorption. The clinical presentation of zinc deficiency includes wide array of skin lesions, growth retardation and hypogonadism [38]. The cell mediated immunity and antioxidants buffer capacity may be compromised as well [39].

#### **4. Neuropsychiatric complications of CD**

There is an established association of CD with different neuropsychiatric symptoms including headache, peripheral neuropathy, ataxia, depression, dysthymia, anxiety and epilepsy [40]. Peripheral neuropathies, characterized by burning, tingling, and numbness in hands and feet is quite common among CD patients and sometimes the initial presentation as well. These neuropathies are associated with deficiencies of different vitamins including B1(thiamine), B2(riboflavin), B3(niacin), B6(pyridoxine), B12(cobalamin) and E, and mineral including copper. However, these deficiencies occurred when there is severe and extensive bowel involvement. Neuropathies may also be associated with lymphoma as well. Patients presenting with neurological manifestation has significant structural and functional brain deficits on MRI as compared to controls. The exact mechanism in relation to depression and epilepsy is not clear yet [41]. Patients with peripheral neuropathies do not responded on gluten free diet as compared to other neurological manifestations.

#### **5. Metabolic bone disease and complications related to joints in CD**

The relationship of bone derangement and CD has been recognized since a long time, and can occur with or without gastrointestinal symptoms (**Table 2**). Low mineral density, reduced bone mass and increased fragility leading to increased risk of fracture is commonly seen in CD. These bone alteration are the consequence of impaired calcium and vitamin D absorption and secondary hyperparathyroidism, resulting primarily from the loss of villous cells in the proximal intestine, where calcium is mostly absorbed accounting for 90% of overall calcium absorption [42]. Minor amount of calcium is absorbed from stomach and intestine, the colon accounts for <10% of calcium absorption. Calcium absorption from intestine,

Factors	Mechanism of action
Hypocalcaemia	Vitamin D deficiency Intestinal mucosal damage Alterations in calcium-transport mechanism Inadequate calcium intake Reduced consumption of dairy products Steatorrhea
Hypovitaminosis D	Alterations in vitamin D metabolism Decreased level of vitamin D-binding proteins Decreased intake of vitamin D Steatorrhea
Bowel inflammation hormones	Chronic release of proinflammatory cytokines PTH Estrogens and androgens
Corticosteroids	Reduction of intestinal calcium absorption Increase of renal calcium excretion Impairment of osteoblast function Alteration of osteoclast resorption cycle
Additional risk factors	Autoimmune alternations Diagnosis in adult life Lapses from GFD Active disease Low BMI Lifestyle factors

**Table 2.**  
*Factors contributing to bone alteration in celiac disease.*

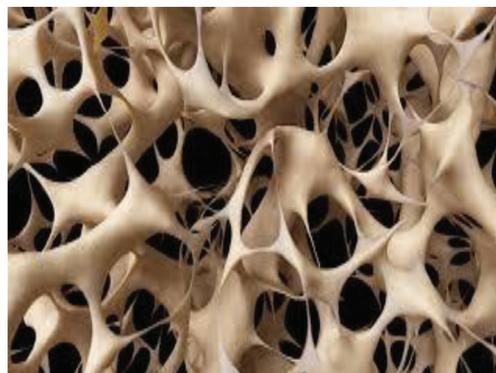
reabsorption from the kidneys and excretion from bones is tightly controlled. Calcium balance is regulated through the calcitropic hormone, parathyroid hormone, 1,25(OH)<sub>2</sub>D<sub>3</sub>, exert complex coordinated activities to maintain normal serum calcium levels [43]. When the extracellular calcium concentration decreases, there is rapid increase in parathyroid hormone release that promotes bone turnover and calcium bone loss. Hyperparathyroidism (**Figure 3**) is common in patients with newly diagnosed CD, 27% in adults and 12–54% in children [44, 45]. It is more common in refractory C, rather than in those who responded on gluten free diet [46]. Low BMD in adult CD patients is related to secondary hyperparathyroidism and osteomalacia due to calcium and vitamin D malabsorption [47]. Vitamin deficiency is present in both females and males accounting for 71 and 64% respectively. Dietary vitamin D is absorbed as a fat soluble vitamin in small intestine, and because of intestinal involvement in CD its absorption decreases thus leading to deficiency of particular vitamin [48]. The other factor of hypovitaminosis is intestinal mucosal lesion [49]. Steatorrhea may also impair the absorption of 25(OH)D undergoing enterohepatic circulation, especially in acute exacerbation of CD. In patients with CD, the regulation of 1,25(OH)<sub>2</sub>D<sub>3</sub> is through genomic action involving the classical vitamin D receptor (VDR), although non genomic regulator is also involved in its absorption [50]. VDR is normally expressed in duodenal mucosa of patients with CD, notwithstanding mucosal damage and atrophy of villi [51]. Although there is no difference in frequency of VDR gene is seen in patients with CD and healthy subjects, therefore VDR gene is unrelated to low BMD [52]. The main factor is reduced calbindin and calcium binding protein due to damaged intestinal mucosa which leads to calcium loss and secondary hyperparathyroidism [53]. In atypical patients of CD, many presented with back pain, diffuse musculoskeletal pain and proximal muscle weakness, due to osteomalacia, osteopenia and osteoporosis. All these patients have low BMD.

Osteopenia is found in almost all patients with CD, either treated or untreated. It is even more common in patients who remained unrecognized. The prevalence of osteopenia and osteoporosis in adult is around 14–35% [54]. Osteoporosis (**Figures 4, 5**) is characterized by low bone mass, micro architectural disruption and skeletal fragility resulting in decreased bone strength and increase risk fracture. It is not only dependent on BMD, but also related to rate of bone formation and resorption, bone size and shape and micro architecture. It has no clinical manifestation until one developed pain due to fracture. The commonest site of involvement of osteoporosis is either lumbar spine or neck of femur or radius. The commonest site of involvement is also lumbar spine accounting almost 26% [48]. The risk is almost doubled as compared to general population. It is more common in peripheral skeleton and common in males with classical presentation than females. Loss of bone density is much increased in older patients with late diagnosis as compared to younger patients and usually not resolved completely with gluten free diet. There is increased fracture risk, almost doubled in CD patients as compared to general population [55].

Children with CD are at risk of reduced BMD, hyperparathyroidism, decreased calcium especially in those with untreated CD [56]. They may or may not have



**Figure 3.**  
*Hyperparathyroidism.*



**Figure 4.**  
*Cross-section of bone tissue-osteoporosis.*

associated gastrointestinal symptoms. There is also risk less-than optimal peak bone mass leading to growth retardation as well. Bone density increases until the end of puberty. If there is lack of achievement of proper peak mass, there is more chance of development of osteoporosis in adulthood [57]. The rate of bone metabolism is also altered in children with CD, which is another factor for osteopathy [58]. In children who are unable to catch up growth need to be evaluated for concomitant growth hormone deficiency, as growth hormone exert its effect on bone mineral density.

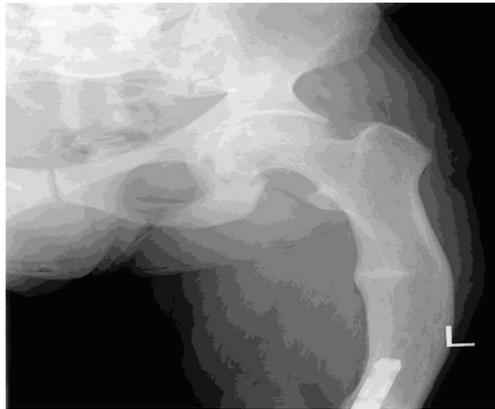
Patients with CD commonly have osteomalacia (**Figures 6, 7**) as well and presenting as aches and pain with bone tenderness unlike to osteoporosis. These patients also presented with proximal myopathy and spontaneous fracture [59]. The exact prevalence of osteomalacia though is not clear in CD [60]. The major factor for development of osteomalacia is decreased absorption of calcium and vitamin D. Diet plays a major and important role in proper bone mineralization. A gluten free diet is low in nutrient, vitamins and minerals, including calcium [61].



**Figure 5.**  
*Radiology-osteoporosis.*



**Figure 6.**  
*Tri-radiate pelvis-osteomalacia.*



**Figure 7.**  
*Looser's zone-osteomalacia.*

Thus they consume less vitamin D and calcium, as compared to normal diet [62]. It further decreases due to lactose intolerance resulting from decreased lactate production by the damaged villi. This factor further decreases BMD, and aggravates osteoporosis and osteopenia.

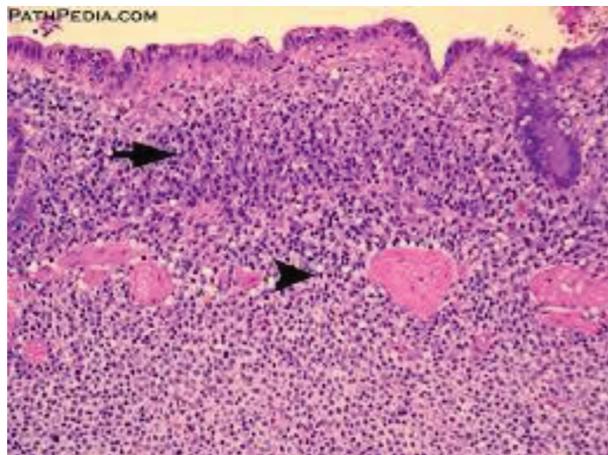
Osteoarthritis is the most common type of arthritis world over. It is inflammatory condition due to damage of cartilage involving any joint of the body. It is commonly presents in patients with CD, but the exact causal relationship is not known [63].

## 6. Malignancies associated with CD

The most important complication of CD is development of cancer. The incidence of gastrointestinal and non-gastrointestinal both is common among CD patients. The commonest among the malignancies is the gastrointestinal lymphomas accounting for 18% of all cancers. The gastrointestinal tract is the predominant site of extranodal lymphoma involvement. Primary lymphomas are less common than secondary lymphomas. Primary lymphomas typically involve any section of gastrointestinal tract from oropharynx to rectum [64]. It can involve single or multiple sites. These are usually non-Hodgkin's lymphomas although Hodgkin's lymphoma has been reported as well. The commonest site of involvement of non-Hodgkin's lymphoma is stomach, present in 68–75%, followed by small bowel than ileocecal junction. Diffuse colonic involvement is present only in 1% [65]. Distribution of primary lymphomas varies among population; gastric lymphoma is more common in United States, while intestinal lymphoma is seen in Middle East and Mediterranean areas. GI Lymphomas are commonly seen in patients with helicobacter pylori infection, autoimmune disease, immunodeficiency and immunosuppressive states, inflammatory bowel disease and CD. Both the T and B cell are commonly seen in patients with CD. The exact etiology of development of these malignancies is under controversy, both the autoimmune and inflammatory factors contribute to the risk. The T cell variant enteropathy-associated T-cell lymphoma (EATL) (**Figure 8**) involving the small intestine mostly, is the commonest malignancy seen in celiac disease, although uncommonly seen [66, 67]. It is most commonly found in adult males with a median age of 60 years. EATL patients mostly presented with acute bleeding, perforation or obstruction, or it should always be suspected if there is clinical deterioration of CD, despite on a strict gluten free diet. It is highly suggested to screen a patient for CD, even if not diagnosed before, if

presented with EATL. Patients with enteropathy associated T cell lymphoma of the small intestine, involving jejunum demonstrates large circumferential ulcer without overt mass. The involved area typically shows lymphoma, while the non-involved sites usually show villous atrophy.

The other variant of EATL, ulcerative enteritis, is another complication of long standing and refractory sprue. It presents with abdominal pain, nausea, vomiting and diarrhea. The other complication of CD includes intestinal ulceration independent of lymphoma and so called refractory sprue and collagenous sprue (**Figure 9**). It is a clinicopathological entity characterized by diarrhea and malabsorption accompanied by the histological findings of subepithelial collagen deposition and severe villous atrophy of small bowel mucosa [68]. The occurrence of collagenous sprue has been seen in patients with celiac disease, tropical sprue, milk intolerance and common variable immunodeficiency states [69]. Regardless of etiology it has a poor prognosis. Collagenous sprue associated with CD usually does not respond to gluten free diet and has a poor prognosis [70].



**Figure 8.**  
*Lymphoma.*



**Figure 9.**  
*Collagenous colitis.*

The risk of other digestive tract malignancies is also commonly seen in CD patients, including oropharyngeal, colorectal, small intestinal adenocarcinoma and hepatocellular carcinomas. In oropharyngeal carcinomas, the commonest is the squamous cell carcinoma. In contrast to gastrointestinal carcinomas, the non-gastrointestinal malignancies, including breast carcinomas are not seen commonly in CD patients. There is no evidence that gluten free diet may decrease the development of malignancies in CD.

## **7. Hyposplenism in CD**

One of the earliest manifestations of CD is hyposplenism, though the exact mechanism of development of hyposplenism is not known. Due to hyposplenism there is increased susceptibility of infection due to encapsulated bacteria especially. Vaccination against prophylaxis for pneumococcus is not highly recommended [71, 72].

## **8. Venous thromboembolism in CD**

Hypercoagulability with elevated homocysteine level and low vitamin-K-dependent anti-coagulant proteins (protein C & S) are relatively common in CD patients. Due to these factors, i.e. increased homocysteine level and decreased protein C & S, along with autoimmunity of CD, there might be increased susceptibility to venous thromboembolism. Although not commonly observed in CD patients [73].

## **9. Kidney disease in CD**

Glomerular IgA deposition is common, occurring in as many as one-third of patients. Although the clinical manifestation is not evident, due to no associated complement deficiency. This indicates that a high circulating load of polyclonal IgA is not adequate to cause nephritis, but other abnormalities of IgA are necessary to translate into mesangial activation and glomerular injury. This mesangial IgA deposition is also seen in healthy individuals from 3 to 16% [74]. Thus its association with other disease is relatively high.

## **10. Idiopathic pulmonary hemosiderosis in CD**

Lane-Hamilton syndrome, the co-existence of CD and idiopathic pulmonary hemosiderosis, is not an uncommon entity in CD patients, although the exact prevalence is not known [75]. It is a rare lung disease characterized by alveolar capillary bleeding and accumulation of hemosiderin in the lungs. Diffuse alveolar hemorrhage is characterized by hemoptysis, dyspnea, alveolar opacities on chest X-ray and anemia. It may lead to iron loss through swallowing of iron-laden alveolar or bronchial epithelial cells. This may lead to functional iron deficiency [76].

## **11. Dental defects in CD**

Oral manifestations are overlooked in CD patients; the long list of clinical signs and symptoms associated with CD includes dental enamel hypoplasia, aphthous

ulcers and delayed eruption of teeth [77]. The dental enamel defects are more common in deciduous dentition. It can involve all four quadrants, but more commonly involved maxillary and mandibular incisors and molars [78]. The exact cause is not understood but it may be due to increased level of HLA DR3 in their blood. This antigen has an association with celiac disease. Dental enamel hypoplasia, a nutritionally related defect of the enamel, presented as pits, lines or grooves on the teeth. Its prevalence ranges from 10 to 97%, and appears to more common in children with CD, as compared to adults [79]. Its prevalence in CD, is much higher than general population, and it is contributed both to nutritional and immunological factors. Another enamel defect, either partial or complete, can sometimes be the only symptoms in children with CD. It is thus advisable to screen children with enamel defects for CD. The other oral manifestation aphthous ulcer or canker sores are also seen in CD, though not specific for CD. Aphthous ulcers, though regresses on gluten free diet [80].

Delayed tooth eruption, another manifestation of CD, has been reported in 27% of patients with CD. The possible cause is probably malnutrition. A high prevalence of enamel hypoplasia is around 66% in CD patients. Formation of plaque is less frequent in patients who are on gluten free diet, probably because of multiple meals in between and use of fluoride toothpaste.

There are other oral problem related to celiac disease, which include recurrent aphthous stomatitis, atrophic glossitis, dry mouth syndrome and squamous cell carcinoma of the oropharynx.

## **12. Reproductive complications in CD**

Females with untreated CD may have multiple complications in relation to reproductive problems. They may have late menarche, recurrent miscarriages, infertility, preterm delivery and low birth weight. These patients may directly presented with these problems and do not have any gastrointestinal issues. All these issues can be resolved with gluten free diet [81].

Males with CD also have infertility, characterized by sperm dysmotility and morphological changes. They may also have androgen resistance leading to infertility. All these can be resolved with gluten free diet [82].

## **13. Cardiac complications in CD**

Autoimmune myocarditis and idiopathic dilated cardiomyopathy are associated with CD, though the prevalence is 5%. Not all patients have gastrointestinal symptoms but almost all of them iron deficiency anemia. These patients responded on gluten free diet with or without immunosuppressive therapy [83].

These patients also have strong association with ischemic heart disease as well.

## **14. Autoimmune diseases in CD**

CD is closely associated with other autoimmune illnesses, like type 1 diabetes mellitus and autoimmune thyroiditis. Type 1 diabetes mellitus and CD has strong genetic association with HLA-DR3, HLA-DQ2, and HLA-DQ8 [84]. Because of the same genetic association, they share same pathogenesis of tissue damage from autoimmunity or intolerance to dietary antigen. The patients with HLA-DQ2 also have raised IgA autoantibodies to tissue transglutaminase and thus likely to have CD with

type 1 diabetes mellitus. Although age of onset of diabetes mellitus is not dependent of CD, neither it triggers the autoimmunity leading to it. Whether a gluten free diet helps in improvement of diabetes mellitus is not clear yet.

There is increased incidence of autoimmune thyroiditis among patients with CD, and hypothyroidism is more common. Association of CD, autoimmune thyroiditis and type 1 diabetes mellitus is part of polyglandular autoimmune syndrome type 111.

## **15. Liver disease in CD**

CD may be associated with nonspecific mild chronic elevation in serum aminotransferase levels. AST ranges from 29 to 80 while ALT from 60 to 130. These increased transaminases may get normalize with gluten free diet. Patients with CD may also have severe liver disease including congenital liver fibrosis, massive steatosis, and progressive hepatitis of unknown origin [85]. There is also an association of primary biliary cirrhosis and primary sclerosing cholangitis with CD.

## **16. Skin manifestation in CD**

Dermatitis herpetiformis in CD is the commonest and pathognomonic skin lesion. It presents usually on external surface in grouped in the form intensely pruritic papules and vesicles. The diagnosis is confirmed on histology by the demonstration of granular IgA deposits along the non-affected subepidermal basement membrane [86]. Similar to CD they have increased antibodies against tissue transglutaminase IgG. Dermatitis herpetiformis and CD, are associated with HLA-DQ alpha beta heterodimers, and may have association with other autoimmune illness as well. It responds well on gluten free diet though requires longer duration.

Patients with CD, also have increased incidence of atopic dermatitis as compared to general population [87].

## **17. Mortality in CD**

There is an increased mortality in patients with CD, due to severe clinical course but as a whole the data is inconclusive. There is twofold rise in death especially in severe disease [88]. The increased mortality is mostly associated with malignant and cardiovascular diseases [89].

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