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CELIAC: AT GLANCE (MINI REVIEW)

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ABSTRACT

Celiac disease is a common chronic inflammatory autoimmune condition caused by intolerance to gluten such as wheat and rye which causes villous atrophy, crypt hyperplasia with infiltration of lymphocytes in genetically predisposed population which is manifested by spectrum of symptoms which varies from mild to signs of malabsorption. Having 0.5 - 1% prevalence in US population and even higher in Africans. Majority of patients express either HLA DQ8 or HLA DQ2 and severity is assessed by Marsh- Oberhuber staging. With the advent of newly serological tests in market for analysis which made the diagnosis as well as screening of patients more accurate like IgA anti-tissue transglutaminase (tTG), which has important component in pathogenesis and diagnosis, IgA anti-endomysial antibodies (EMAs) and total IgA level. Duodenal biopsy are still considered for diagnosis, but in clinical practice in certain circumstances specially, in children diagnosis is made without biopsy. Gluten free diet plan is highly strict, very expensive, socially isolating and mandatory which shows clinical in addition to histological improvements and also reduces complications as well as malignancies. Several years needed for the mucosa to emerge into normal on biopsy. These days high level research is going on for the development of non-dietary approaches, few are under clinical trials with the hope that it will give some kind of advantage to control celiac disease.

KEYWORDS: CD Celiac disease, IEL Intraepithelial lymphocytes, IgA tTG Immunoglobulin A Tissue transglutaminase, IgA EMA immunoglobulin A Endomysial antibody, AGA Antigliadin antibody, DGP Deaminated gliadin peptide.

INTRODUCTION

Celiac disease is a chronic inflammatory immune mediated disorder which occurs in genetically predisposed population. Celiac disease is the interaction between gluten and 3 predominant factors [immune, genetic and environmental factors]. In celiac disease there is infiltration of intraepithelial lymphocytes [IELs] in the epithelium and plasma cells in the lamina propria with crypt hyperplasia. Villous atrophy occurs in celiac disease due to abnormal cellular response and resolves with gluten free diet. Celiac disease is caused by gluten (major component of wheat) and other proteins in barley, rye and oats which are broadly consumed cereals in most international locations. As we know, wheat, Barley and Rye contains gluten, hordein and scalin respectively, are derived from the Triticeae tribe of grass [Gramineae] family. Figure1

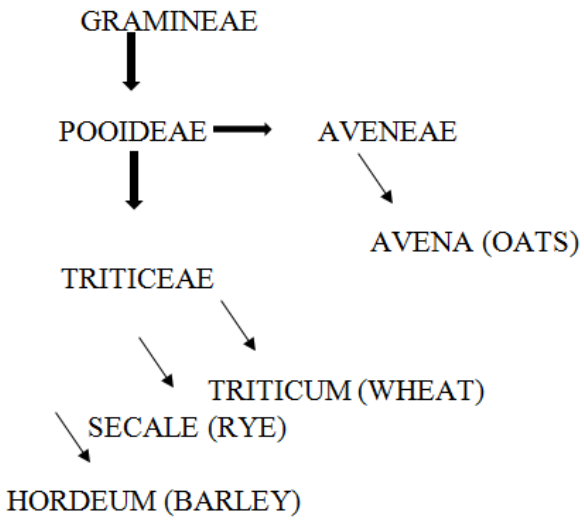


FIGURE 1

The gluten content of different grains are described by Gliandins or Glutenin having different concentrations among plant species. Table 1.

TABLE: 1Gluten content of Wheat, Rye, Oats, Rice.

FOOD	TOTAL PROTEIN	GLIADINS	GLUTENINS
WHEAT	10-15	40-50	30-40
RYE	9-14	30-50	30-50
OATS	8-14	10-15	~5
RICE	8-10	1-5	85-90

Gliadins and Glutenins (% of total protein)

Patients may be asymptomatic or presents some classical symptoms like signs of malabsorption such as chronic diarrhea, bloating, weight loss, abdominal pain and some silent clinical features which are iron deficiency anemia, osteoporosis, gastroesophageal reflux, constipation, weight loss, neurological symptoms, dermatitis herpetiformis, hypoproteinemia, hypocalcemia, elevated liver enzymes levels, type1DM and gluten ataxia.[1] Gliadin is alcohol soluble fraction of gluten that is highly resistant to degradation by intestinal proteases due to enriched in glutamine and proline residues. After degradation of long fragments (10-15 amino acids), gluten stays in the upper GIT tract which reach in lamina propria and activates innate and adaptive immune system.

HISTORICAL ASPECTS

Celiac disease has an ancient history back to first century A.D. Symptoms of celiac disease were first explained by a Greek Physician, Aretee de cappadoce in the first century. His writings explained as unnamed disease and he named as "Koiliakos'' while describing in his patients which has meaning "suffering in the bowels". Francis Adams translated this name from Greek to English for the sake of Sydenham Society of England as "Celiacs" or "Coeliac disease". Samul Gee clarified the description in 1888 that diety treatment might be helpful. But role of triggering of gluten peptides was identified in 1950. Willian Dicke in 1950 confirmed in his thesis that exclusion of wheat, rye and oats from diet lead to dramatic improvement in the disease symptoms and also proposed a gluten free diet which is still an effective treatment of CD. [2] Margot Shiner in 1957 reported specific lesions observed in CD. Early 1990s discovery of the highly specific and sensitive antibodies has changed the diagnostic field of celiac disease.

SEARCH STRATEGY AND SELECTION CRITERIA

We searched PUBMED, MEDLINE and some other sources also using the headings ''coeliac disease'' and ''celiac disease'' for articles published till Sep 2016. We also searched the references lists of review articles of celiac disease extensively and considered the older publications also.

EPIDIMIOLOGY

The prevalence greatly varies from one country to other country and even within the country. The average occurrence of celiac disease in world ranges from 1% - 2% in general population. There were 3 studies conducted inside the Europe which clearly specified about the prevalence rate which were higher than 1/66; United kingdom[3], Germany[4] and Sweden.[5] Europe and united states has similar average prevalence in CD. In last few years prevalence is increased due to great awareness through information campaigns and internet active groups. Due to lack of data in Asian population including Chinese population has low prevalence of CD due to mainly rice based food. There is no formal epidemiological studies has been performed in china.[6],[7] There are two peaks of frequency in CD has been noticed between 1 to 2 years of age and second near 30 years of life. The first top peak is due to the introduction of many infections and food allergens. There is 2 to 3 fold increase of CD in women as compared to men in adult whereas sex ratio in children is 1/1.[8] The reason of high fold as compared to men in 30 years are due to strong ovarian activity.

DIFFERENTIAL DIAGNOSIS

As we clearly knows about celiac disease presents as marked villous flattening and increased intraepithelial lymphocytes [IELs]. When there is negative serology, other diseases should be properly ruled out which has similar type of features.

TABLE2

D/D OF CELIAC DISEASE

TROPICAL SPRUE
COLLAGENOUS COLITIS
WHIPPLE'S DISEASE
GIARDIASIS
VIRAL ENTERITIS
AIDS
CHRON'S DISEASE OF THE SMALL INTESTINE
SMALL INTESTINAL LYMPHOMA

CARBOHYDRATE INTOLERANCE
COW'S MILK INTOLERANCE
AUTOIMMUNE ENTEROPATHY
GRAFT V/S HOST DISEASE
RADIATION DAMAGE
ANOREXIA NERVOSA
BACTERIAL OVERGROWTH
HYPOGAMMAGLOBULINEMIA
IRRTIABLE BOWEL SYNDROME
TUBERCULOSIS
ZOLLINGER-ELLISON SYNDROME

CLINICAL FEATURES

While describing clinical presentation, celiac disease is divided into four subgroups named as; 1) Classic disease 2) Atypical disease 3) Asymptomatic (silent) 4) Latent disease [often difficult to differentiate from silent type]. Classic disease has three features; Firstly malabsorption with diarrhea particularly steatorrhea, loss of weight, vitamins and nutritents deficiencies. Secondly; serological studies +ve with classical pathological findings of villous atrophy. Thirdly; resolve with the proper gluten free diet. Atypical disease has common minor symptoms making the diagnosis more difficult.[9] Minor symptoms such as fatigue, anemia, arthritis, enamel defects, abnormal transaminases, osteoporosis or infertility. In this group most patients are serologically positive and show typical features on biopsy. Patients are asymptomatic in silent disease but they show villous atrophy and may have crypt hyperplasia on histological examination whereas there is isolated increased of intraepithelial lymphocytes in latent disease (considered as a pre-pathologic state) with a risk of evolution towards silent or symptomatic disease. Conversely, evolution towards latency has been described in other forms of CD.[10] Patients which comes in category of latent disease have minor or no symptoms while on gluten containing diet and have normal jejunal mucosa. It can be divided into 2 subtypes; patients consuming gluten containing diet, have normal mucosa but celiac disease develops later and those patients who present celiac disease in childhood, recover on gluten free diet. Later remains silent when gluten is reintroduced into the diet and approximately 20% remains silent others represents villous atrophy. Celiac disease is a complex Clinico-pathological diagnosis. There is a great communication required between clinician and pathologist.

American college of Gastroenterology guidelines (2009) suggests about the screening of patients with diarrhea or mixed [means alternating diarrhea with constipation (IBS)] due to one serological study found that Celiac disease is 4 to 5 fold more common in IBS.[11] An observational study done in adult Chinese patients with diarrhea predominant irritable bowel syndrome showed that prevalence of celiac disease in patients with IBS-D is 1.01% (4/395) and 0.28% (1/363) in the control group.[12] A Multi centric United States based study compared 492 IBS patients with 458 controls and found same prevalence as in general population.[13] May be screening is justified due to high prevalence (1/132) in European population and white North Americans. Conditions associated with celiac disease are divided into two categories; a) Gastrointestinal: Dental enamel defects, recurrent aphthous ulcers, atrophic glossitis (sore/burning mouth) which respond to gluten free diet. There is high symptoms of GERD in celiac patients which has been proved in a study which compared 133 celiac patients with 70 controls [14] and when they are put on gluten free diet for 3 months their symptoms were comparable with control group. One study reported that there is high incidence of esophagitis in celiac disease with a sex and age adjusted standardization ratio of 16.0 (95%CI,8.7-25.5).[15],[16] A case control study done in Sweden which showed that pancreatitis has an increased risk in celiac disease.[17] So without finding any cause of pancreatitis we should think about CD. Autoimmune hepatitis, steatosis, primary biliary cirrhosis and primary sclerosing cholangitis are also associated with CD. Inflammatory bowel disease may be associated with celiac disease which was proven in many case series whereas ulcerative colitis often more common than crohn's disease. Celiac crisis (rare) which presents with severe type of dehydration, renal dysfunction and sometimes with extreme metabolic disturbances may requires extensive care [Hospitalization: corticosteroids, peripheral nutrition]. These type of situations are mainly precipitated by gluten challenge.[18] b) Non-Gastrointestinal: In celiac disease there are many Non-GI presentations and associations. Most common are iron deficiency and metabolic bone diseases. Iron deficiency is mainly in those who are refractory to therapy. Celiac disease has low threshold for osteopenia and osteoporosis. A study compared 77 patients of celiac disease with 157 controls and found that there was significantly low bone density in lumbar spine and femoral neck (-6% and -5% respectively). In celiac disease osteoporosis of lumbar spine is more common (26%vs5%).[19] Hyperparathyroidism, Peripheral neuropathy usually occurs in 50% celiac disease patients before the diagnosis is established. A Sweden based study showed that there is a later occurrence of Polyneuropathies other than neurological problems.[20] Infertility is found in both sexes. Men usually has low sperm counts.[21] Low birth weight or greater rate of abortions or un-favourable outcomes in pregnancies are seen in untreated female celiac patients.[22]

WHO MAY REQUIRE TESTING FOR CELIAC DISEASE

A) Gastrointestinal
B) Non gastrointestinal
C) Associated conditions
D) Associated malignancies

TABLE 3

GASTROINTESTINAL	
AREA	**CONDITIONS**
ORAL	DENTAL ENAMEL HYPOPLASIA, ATROPHIC GLOSSITIS, APHTHOUS ULCERS.
ESOPHAGUS	GERD, EOSINOPHILIC ESOPHAGITIS.
LIVER	AUTOIMMUNE LIVER DISEASE, INCREASED HEPATIC TRANSAMINASE LEVELS, PRIMARY BILIARY CIRRHOSIS, PRIMARY SCLEROSING CHOLANGITIS.
INTESTINAL	IBD (UC>CD), CHRONIC DIARRHEA, CHRONIC ABDOMINAL PAIN, MALABSORPTION, BLOATING, ERRATIC BOWEL HABIT, CONSTIPATION (COMMONLY SEEN IN CHILDREN).
OTHERS	ANOREXIA, VOMITTING.

TABLE 4

NON-GASTROINTESTINAL

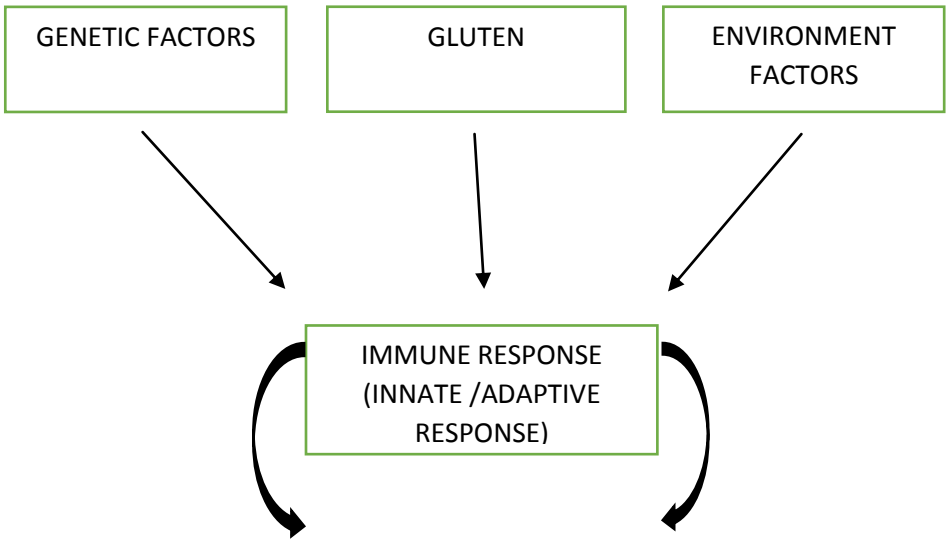
SYSTEM	**CONDITION**
DERMATOLOGY	DERMATITIS HERPETIFORMIS.
HEMATOLOGY	DEFICIENCY (IRON, B12, FOLATE, VIT E, VIT K), HYPOSPLENISM.
ENDOCRINOLOGY	AUTOIMMUNE THYROID DISEASE, TYPE 1 DIABETES.
GYNECOLOGICAL	DELAYED PUBERTY/MENARCHE, AMENORRHOEA, EARLY MENOPAUSE, INFERTILITY (BOTH SEXES).
IMMUNOLOGICAL	SELECTIVE IgA DEFICIENCY

TABLE 5

ASSOCIATED CONDITIONS	**ASSOCIATED MALIGNANCIES**
FAMILY H/O OF CELIAC DISEASE	SMALL BOWEL LYMPHOMA
PERIPHERAL NEUROPATHY	SMALL BOWEL ADENOCARCINOMA
OSTEOPENIA/OSTEOPOROSIS	LARGE BOWEL CARCINOMA
SHORT STATURE	HODGKIN'S LYMPHOMA
UNEXPLAINED ALOPECIA	NON-HODGKIN'S LYMPHOMA
SJOGREN SYNDROME	OROPHARYNGEAL CARCINOMA
DOWN SYNDROME	PRIMARY LIVER CARCINOMA
TURNER SYNDROME	ESOPHAGEAL LYMPHOMA
WILLIANS SYNDROME	

CAUSATION AND PATHOGENISIS

Celiac disease occurs as a consequence, due to participation of three main factors which are described as a triad of Genes, Gluten and Environmental factors. Figure2



1) Autoantibodies (TTG, EMA)
   Detected by serological tests.
2) IEL and Villous atrophy
   Detected by Histopathologically and Endoscopically.
3) Gastrointestinal and Extra-intestinal features.
   Detected by clinically and by other tests.

FIGURE 2

GENES

Celiac disease is an autoimmune disease of GIT (gastrointestinal tract) which primary affects small intestine by causing atrophy of villi.[1] It is polygenic, multifactorial and autoimmune disease. Development of CD in an individual requires both components which means exposure of gluten in diet as well as having genetic predisposition either in the form of HLA-DQ_2 or HLA-DQ_8.[23] Majority carry [> 90%] HLA DQ2 haplotype (DQA1*0501, DQB1*0201 heterodimer) and remaining carry HLA DQ8 (alpha 1*0301, beta 1*0302).[24],[25] The genetic risk due to HLA genes are between 40% to 53%[26] and rest are due to Non HLA genes. The concordance rate of monozygotic twins are better or higher than MCH identical siblings (70% and 30% respectively). It is noticed that only 1 in 100 develop CD who carry HLA-DQ2 even 30% caucasians carry this gene. Recently studies invented some new genes that are involved in the pathogenesis of CD including COELIAC337 and COELIAC438 at positions 2q33 and 19p13.1.

GLUTEN

Apart from genetic involvement, role of dietary gluten which is the major constituent of many grains and plays an important role in the development of CD. Gluten contains gliadins monomeric proteins and glutenins polymeric aggregated proteins. These peptides are rich in alcohol-soluble proline and glutamine residues which are poorly digested by the human gastrointestinal tract [27]. Specific proteins molecules known as prolamins which are present in wheat, rye and barley. Prolamins are present (high amount) in proline and glutamine amino acids which serve as the main casade of events in celiac disease. Gluten is not found in rice, maize and millet. There is association of oats with celiac disease due to cross-contamination with other cereals at the time of milling.[28] Human consume gluten which is partially digested in the form of gliadin fragments and enters through the epithelial barrier of intestinal mucosa. There is alteration in the gliadin peptides present in gluten via TTG enzyme with in the lamina propria that causes immunopathogenesis. Tissue transglutaminase which is also deaminated the gliadin and makes it more immunogenic molecule. Actually there are aggregation of environmental and genetic factors which makes gliadin peptides as foreign bodies and activate immune response which cause inflammation, intestinal in addition to histological changes.

ENVIRONMENTAL FACTORS

Environmental factors plays vital role as compared to genes which were described as a fact that HLA-DQ2/DQ8 carriers which are nearly 30% of population who are exposed to gluten don't have disease while 1% population only have CD. There are various environmental factors which plays important contribution in the pathogenesis of CD ranging from

Vitamin D to season of birth. Early life factors which includes breast-feeding, infections and alterations in the intestinal microbiota that influence the intestinal environment. Infancy and adulthood infections of gastrointestinal tract are considered the main risk factors for later development of CD. [29] Even some studies do not support these infections theory of infancy and adulthood.

PATHOLOGY

While beginning discussion regarding pathology, some important features we should know that suggest celiac disease such as proximal small bowel involvement (Descending duodenum is more involved than distally), few cases shows patchy distribution, mucosal appearance changes which includes villous atrophy, crypt hyperplasia, basement membrane thickening, reduced number of goblet cells, inflammation of mucosa, increased IELs, influx of immune cells in the lamina propria, enterocyte changes, cuboidal morphology, loss of basal nuclear orientation, cytoplasmic vacuoles.[30] When biopsy is planned take care of two important points:

1) Patient must be on gluten containing diet for at least 2 to 8 wks.
2) Four to Six exact pieces of biopsy are mandatory for proper endoscopic sampling which should be inclusive of duodenal bulb samplings, in order to diagnose the patchy disease process.[31],[32]

IELs are minor lesions though considered as important for diagnosis but isolated infiltrative lesions has low specificity for CD. Recently other causes of IELs have been reviewed.

The modified Marsh–Oberhuber classification
• Type 0: Normal crypts and villi, IEL<40.
• Type 1: Basically who are gluten free diet or minimal amounts of gluten being ingested, patients of dermatitis herpetiformis, family persons of CD patients, may be in infections, >40 IELs, normal crypts and villi.
• Type 2: Rarely seen in dermatitis herpetiformis, increased IEL >40, hypertrophic crypts and normal villi.
• Type 3: Spectrum of changes seen in symptomatic CD. IEL are >40 and hypertrophic crypts but:
3a) has mild atrophy of villi
3b) has marked atrophy of villi
3c) has total atrophy of villi
• Type 4: IEL<40, normal crypts and total atrophy of villi
Simplified system proposed by Corazza, Roberts and Ensari which is based on three morphological features
• Grade A = Infiltrative non-atrophic lesions.
• Grade B1= Atrophic lesions with shortened but still detectable villi.
• Grade B2= Atrophic lesions with undetectable villi.

This Corazza and colleagues system has higher inter-observer reproducibility than Marsh-Oberhuber classification. The patients with silent or minor celiac disease their assessment is not easy or difficult and post treatment biopsy may be beneficial. Repetition of biopsy after celiac disease food introduction is not always mandatory but if we want to go for it then gives an important information regarding histological improvement in terms of diagnosis, dietary compliance and reassures the patient. One important point is that sometimes a second biopsy plays pivotal role in diagnosing CD in those patients in which investigations are negative or discrepant serology or continued symptoms. Endoscopically two main changes has been recognized: 1) Disappearance or reduction of Kerckring.[33] 2) Scalloping of reduced folds.[34] These type of endoscopic changes have no role in diagnosing the CD when disease is suspected on clinical or serological grounds. This means decision to do biopsy does not depend on endoscopy but while doing endoscopy for other causes, these findings might be a crucial step for patients in whom disease is not suspected.

MANAGEMENT: DIAGNOSIS AND TREATMENT

Diagnosis of CD includes three steps:
• Blood tests positive.
• Biopsy and histological confirmation (small bowel).
• Response to gluten-free diet.
There are accurate and multiple tests that are available in the market. Different types of tests which are used to diagnose celiac disease are discussed.

In late 1990 tTG (anti-tissue transglutaminase antibody) was identified and developed as a high accuracy ELISA based test in CD. In previous years guinea pig antigen was used which showed higher false-positive rates. Now a days a new recombinant protein based antigens are used which is far better than previous Guinea pig based antigen. IgA-tTG test is a preferred serological test in persons whose age is over 2 years for diagnosis of celiac disease.[35] IgA-tTG antibody shows very high rates of negative predictive value but there are few conditions such as enteric infection, congestive heart failure, chronic liver disease and hypergammaglobulinemia in which false positive results can occur.[36] Before the development of IgA-tTG, IgA-EMA (anti-endomysial antibody) antibody was used as the first diagnostic approach. Disregarding the fact that this test has some technical issues and inter-observer as well as inter-site variability has been found, still it is considered to be the most sensitive test even by the well-established labs. [37] tTG gluten peptides (after removal of the amine group) of small intestine binds to HLA-DQ2 or DQ8 on APCs and initiates T cell response. This test is considered as a preferred test in persons having IgA deficiency and there is one more quality of this test is that it is more sensitive in children less than 2 years when compared to tTG.

In clinical practice we conduct two tests; immunoglobulin A-tissue transglutaminase (IgA-tTG) and total serum IgA (high prevalence of IgA deficiency) in patients with celiac disease. If outcomes of both tests

are negative then it seems that celiac disease is unlikely, but if clinical symptoms shows suspicion for the disease then next test is IgA-EMA. A duodenal biopsy is warranted for definitive diagnosis under consultation of GI specialist, if in case IgA-tTG or IgA-EMA comes out to be positive. IgA deficiency has been observed in those patients in whom a negative IgA-tTG test and low levels of total serum IgA were found; in these cases the next test should be immunoglobulin G (IgG). If IgG test is negative then celiac disease is unlikely but if it is positive then a tissue biopsy of the small intestine is essential for diagnosis. Patients in whom low levels of IgA are found, IgG based DGP or tTG should be advocated and according to a new study IgG anti tTG has been found to be more specific than IgG anti DGP but is less sensitive for diagnosing celiac disease.[38] Antigliadin antibodies (IgA-AGA/IgG-AGA) are not used for initial testing due to low sensitivity and specificity and other limitation of these antibodies are that they may also be found in healthy individuals as well as in inflammatory bowel diseases patients. A new test to diagnose celiac disease is Deaminated gliadin peptide which has great significance in those patients having IgA deficiency which is nearly 10 to 15 times more common in celiac patients. Results of serological tests in Children <5 years may not be reliable and less accurate in <2 years.[36] Outcomes of different serological tests in terms of sensitivity / specificity (IgG DGA 80%/98%, IgA EMA >90%/>95%, IgA DGA 88%/95%, IgA tTG 95%-98%/94%-95%, IgA AGA 80%-90%/85%-95%, IgG EMA 40%/95%, IgG tTG 40%/95%, IgG AGA 80%/80%) to diagnose celiac disease.[36],[39],[40]

TREATMENT

Established treatment is Gluten free diet which is considered as a basic treatment of celiac disease and should be recommended after the diagnosis has been made (established).The gluten free diet is without wheat, rye, barley and spelt(which is also a wheat variant). Actually oat is a kind of cereal which is tolerated by most of the celiac disease patients but few sporadic cases has been found with oat intolerance. Secondly, it has been noticed that during marketing many oats products has been mixed with some other cereals. Cereals (maize, rice, sorghum, tef), meats, dairy products, fruits and vegetables which are well tolerated by the celiac patients. Beer is a source of gluten due to its protein content from malted barley. Gluten is also present in medications, vitamins and minerals in a form of its inactive ingredients and due to no specific regulations their concentration varies. Physicians should tell their patients about few important things of gluten free diet which are; 1) Gluten free diet is not easy. 2) Expensive. 3) Not as tasty as normal diet. 4) Lifelong commitment is important. It is not feasible for total elimination of restricted food products but strict restriction is important for achieving the goal or outcome. It is difficult to assess the amount of gluten to be tolerated and varies from person to person. A study showed that patients can tolerate 50mg of gluten /day. On contrary, a recent study recommends less than 10mg is safe and fewer significant abnormalities has been seen. [41],[42] Dietary education should be mainly concentrated on eating outside, eating during travelling, planning of balanced diet and hidden sources of gluten. Celiac disease patients should discuss about their food with a registered dietitian. Now a days many specialized celiac disease websites are there which are ready to help patients like American Dietetic Associations Consumer Nutrition (hotline@eatright.org), Celiac Disease Foundation (http://www.celiac.org). Adequate replacement of vitamins and minerals should be added for healthy and balanced diet. Nearly 10-30% patients in spite of 12 months of gluten free diet they have persistence of symptoms, abnormal laboratory findings and even have clinical signs are classified as Non-responders celiac disease [NRCD]. These patients are mostly due to in advertent exposure to gluten which accounts nearly 35-50%. Lactose and fructose intolerance, small intestine bacterial overgrowth (SIBO) and irritable bowel syndrome (IBS) should be considered while making the differential diagnosis of NRCD. A number of studies have done till date to assess the outcomes of gluten free diet. In a cohort study done by Patwari et al [43] they observed that there was improvement in nutritional as well as in hematological status of the patients those who were on gluten free diet. Shahbazkhani et al showed in their study that patients of IBS, diagnosed with celiac disease were benefited by following gluten free diet and showed improved symptoms.[44] Study done by Curione et al [45] reported 3 patients of celiac disease with idiopathic dilated cardiomyopathy offered a gluten free diet and great results came which showed improvement in ECG parameters as well as cardiac symptoms and reverse results was noticed who did not adhere to gluten free diet and even supplementary drug was added which was necessary for their symptoms. Six months of gluten free diet showed reduction in hepatic enzymes such as transaminases as observed by Yolta et al.[46]

OTHER MEASURES

1) **Manipulation in diet**: As it is known that, gluten acts as a major protein matrix. Gluten detoxification was successful via targeted mutagenesis.[47] There is different perception in the general population about this, genetically modified wheat. This transgenic change does not satisfy the people due to traditional as well as historical beliefs in elasticity of the product in the form of its viscoelastic network of Dough which is considered for strength. Sorghum is safe in celiac patients which is closely related to maize. There is a new dietary opportunity for celiac disease patients in the form of Triticum Monococcum which is considered as the oldest and primitive cultivated wheat. Triticum Monococcum showed lack of toxicity in vitro studies. An experiment vitro based study done in which copolymer of hydroxyethylmethacrylate and sodium4-styrene sulfonate is used which prevented

the gliadin induced epithelial toxicity. There is another approach used in which decapeptide from durum wheat acts as an antagonist against the act of gliadin toxicity and considered as a protective role in celiac disease.[48],[49]

2) **Degradation of gluten enzyme**; An Alternative oral therapy which prevents the toxigenic as well as immunogenic activities by abolishing the gluten enzyme reaction (enzyme degradation). In experimental vivo based study it is noticed that Prolyl endopeptidase (gliadin detoxifer) is used, no malabsorption is noticed in most patients after 2 wks of gluten challenge. [50],[51] A combination therapy (glutamine specific endoprotease and prolyl endopeptidase) was rewording in rats. To block the T-cell mediated gliadin activity, wheat flour is pretreated with microbial tTG.[52] Three randomized controlled studies proved that probiotic bacteria (lactobacilli) has better tolerance in humans to reduce gluten toxicity (vivo study). VSL#3(probiotic) breakdowns peptides of gliadin.[53]

3) **Permeability Inhibition**; AT-1001 is a protein extracted from vibrio cholera which acts by inhibiting cytokine production, thus reducing the intestinal permeability hence improving the symptoms in celiac patients.[54]

4) **tTG inhibition**; Blocking the activity of tTG helps by two mechanisms. Firstly, it checks the pro-inflammatory response; secondly, it decrease the immune response to gluten. KCC009 inhibits tTG2 (per os), has short term effects and appears to be promising; though further studies are required.[55]

5) **Anti-inflammatory cytokines**; Activation of T-cell caused by gluten are prohibited by interleukin-10.[56]

6) **Gluten peptide vaccination;** An integration of immune dominant α and ω gliadin 17- mer peptides is under clinical trial to form a gluten peptide vaccine.[57]

7) **Immune modulation;** Immune modulation by Necator Americanus is under phase 2 clinical trial. The idea is to alter the local immune response as well as to suppress gluten sensitivity in patients of celiac disease. This treatment might be helpful in inflammatory bowel disease patients if the outcomes happen to be positive but further testing will be needed.

8) **Lymphocytic recruitment blockage**; CCX282-B agent is under phase 1 which blocks innate immune response by anti-CCR9 blockage mechanism.

PROGNOSIS

Nearly 90-95% patients who follow gluten free diet show clinical improvements within days to weeks but histological improvements will take more time (months to years) as compared to clinical. If IgA tTG levels does not decrease after six months this suggest that the patient is taking gluten either directly or by indirectly means. Both education and assessment are equal important for proper compliance and should be done for patient and their family. Repeat endoscopy is not needed to check response but serum test should be followed to check antibodies every 3 to 6 months till normalization occurs.[58] Repeat biopsy should be considered in a situation where antibodies level are still elevated even after adequate dietary treatment of 6 to 12 months.[58] Depression is routinely comorbidity which frequently encountered with this chronic disease for which patients must be routinely monitored and managed accordingly.[59] Approximately 5 percent patients comes under refractory celiac disease which requires potential treatment such as corticosteroids or immunomodulators.

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Competing interest

No conflicts of interest for this article.

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