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Celiac Disease and Its Clinical Manifestations

Poornima Sharma[1], Shaik Khasimbi[2], Sharad Wakode[3,*]

[1]Department of Quality Assurance, Delhi Institute of Pharmaceutical Sciences and Research, New Delhi, India
[2]Department of Pharmaceutical Chemistry, Delhi Institute of Pharmaceutical Sciences and Research, New Delhi, India
[3]Department of Pharmaceutical Chemistry, Delhi Institute of Pharmaceutical Sciences and Research, New Delhi, India
*Corresponding author: sharadwakode@gmail.com

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Abstract Celiac disease (CD) is associated with activation of the immune response toward specific protein commonly known as gluten, Which causes damage to the small finger-like projections called villi. Samuel was the first person who describes the disease in the year 1887. The given review article describes various factors which are associated with CD such as genetic factors, environmental factors and proteins. Chronic diarrhea, Hypochromic anemia, Short stature, Bone loss, Recurrent abortions, Hashimoto's disease, etc are some common clinical manifestation. Along with clinical manifestations, we will also discuss the diet for the patients and treatment approaches.

Keywords: *celiac disease, autoimmune disorder, small intestine, gluten, villi*

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1. Introduction

Celiac disease (CD) is categorized as a disorder in which a protein known as gluten activate the immune response in the human body. It causes damage and swelling to the small intestine. In the united state, nearly 1% of the total population suffers from CD and one in a hundred people worldwide. The celiac disease comes under the category of autoimmune disorder. The person who has CD eat gluten, it generates the immune response which starts attacking the small intestine. This attack may lead to damage of villi, which is a small finger-like projection found in small intestine responsible for nutrient absorption due to its large surface area. CD can evolve at any age after people start eating gluten-containing medicine and food. If left untreated, it can lead to other additional health issues including reduced bone density, cancer, infertility and other autoimmune diseases. Sometimes CD is also known as gluten-sensitive enteropathy or celiac sprue. It affects men and women of all ages and races. Curative medication is not available for CD, however, most people follow the inflexible gluten-free diet which helps in the management of symptoms and it also promotes healing of small intestine. The most common symptom irritability mainly occur in children. The protein is responsible for the CD found in rye, barley and wheat. Other products which contain gluten are vitamins and their supplements, hair and skin products, lip bam and toothpaste. Awareness and celiac diagnosis program provide good results. From last few years, the sale of gluten-free products reached more than $5 billion. The first condition resembling CD was reported by Aretaeus and Cappadocia in the 2nd century AD [1]. McDonald et al. In 1965 demonstrate the genetic association of CD [2]. The description of the mucosal transformation characteristic of CD reveals by Benecke in the year 1910 [3]. In CD, there is a selective deficiency of IgA reported by Mawhinney and Tomkin in 1975 [4]. There is a close association between HLA-D and CD demonstrate by Howell et al. in the year 1986 [5]. The cytokine release in CD triggered by gliadin express by Ferguson et al. in the year 1975 [6].

2. History

Samuel gee was the first person who describes the CD in the year 1887, he described some of the clinical symptoms of a disease like poor growth, fatigue and diarrhoea. Gee stated that the treatment of CD is based on a gluten-free diet. The extensive flattening of villi and chronic inflammation of the small intestine are found in biopsy samples of the patient suffering from CD demonstrate by Paulley [7,8].

3. Epidemiology

The study reported that a high prevalence of CD was found in western Sahara people. India, Scandinavia, middle east and north Africa are some countries which show high prevalence. 1% population of Europe and the United state suffers from CD. The Mucosal Biology Research Center established in the USA for CD. Women are slightly more likely to be affected by the CD as compared to males.

4. Gluten Sources

The Gluten sources and their derivatives include; oats (oat flour, oat bran, oat gums, oat fibre and oat groats), wheat (sauces, gravies, wheat flour, wheat starch, soups, processed meats and fish, wieners, graham flour, wheat germ,etc.), barley and malt (beer, malt, malt syrup, malt extract, cereal), Rey(cereals), semolina (pasta), farina (pasta).

5. Gluten-free Food

The gluten-free foods are fruits, vegetables, unprocessed meat, almonds, peanuts, cashews, pistachios.

6. Different Types of Celiac Disease

CD is categories into five different types on the bases of positive serological markers and bowel villous atrophy. These five types are;

1. Classic celiac disease
2. Non-classic celiac disease
3. Silent celiac disease
4. Potential celiac disease
5. Refractory sprue celiac disease

The symptoms of the classic CD include malabsorption and mainly occur in the age groups 6-24 months [9]. Iron deficiency anemia is one of the symptoms of the non-classic CD which occurs due to iron and folate malabsorption in the jejunum. This CD is more common than classic CD [10]. Silent CD doesn't show any symptom. Positive serum markers and normal bowel biopsy are the identification measures of potential CD. The refractory CD is divided into two main groups; the first one is primary refractory CD (no good response to a gluten-free diet) and the second one is secondary refractory CD (good response to a gluten-free diet).

7. Factors Involve in Celiac Disease

There are three main factors involved in the development of CD (Figure 1).

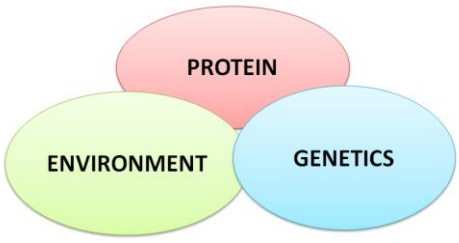

Figure 1. Factors involve in celiac disease

7.1. Gluten (Protein)

The gluten is the main reason behind the CD. It contains proline and glutamine. Due to its viscoelastic and adhesive property, it is widely used in the food industry and for non-food products. In few people, gluten triggers autoimmune, inflammatory and immunological reactions. It can also rise various gluten-related disorders like a CD which affect 1-2% of the general population, non-coeliac gluten sensitivity in 6-10% of the general population, gluten ataxia (indigestion of gluten), dermatitis herpetiformis and other neurological disorders [11,12,13,14]. wheat, barley, rye and oats are the main source of gluten. The undigested fraction of gluten is gliadin which shows resistance toward degradation by pancreatic, gastric and intestinal brush border membrane proteases in the intestine due to which it stays in the lumen for a long time after gluten ingestion [15]. They start the interaction with antigens present in lamina propria when they travel through the epithelial barrier of intestine mainly when a person suffers from intestinal infection or may have increased intestinal permeability.

7.2. Genetic Factors

The CD mainly triggered by intolerance to protein (gluten) in genetic susceptible human being carrying the HLA-DR3-DQ2 and DR4-DQ8 risk haplotypes [16]. The HLA complex involves in CD consists of 47 Mb on chromosome 6p21. Studies suggest that the contribution of the genetic factor in CD is less than 50% [17]. There are some non-HAL genes which influence the susceptibility of disease, but this is not confirmed yet.

7.3. Environmental factors

Epidemiological studies suggested that there are certain environmental factors which play an important role in the development of the celiac disease. The risk of development of celiac disease increase with the administration of gluten before four months of age [18]. The introduction of gluten after seven months is associated with marginal risk. The rotavirus infection in infants increases the risk of CD [19]. There is the number of diseases which increase the risk of CD some of them are Type 1 diabetes mellitus, Down syndrome, Selective IgA deficiency, William syndrome, Turner syndrome, First-degree relative and Thyroiditis [20].

8. Autoimmunity in CD

CD is trigger by gliadin and some related cereal proteins. Some patients show clinical and histological improvement when gliadin and related cereal proteins are eliminated from the diet. The active disorder is in the course of mucosal (especially human gamma globulin [Ig] A) autoantibodies to reticulin, a standard constituent of the animate thing matrix. Antireticulin autoantibodies area unit similar to anti endomysial, antijejunal or anti-umbilical twine antibodies [21,22,23] immunoglobulin A anti endomysial autoantibodies (EMA) allow screening for biopsy-proven disorder with AN almost 100 per cent sensitivity and specificity [24]. For classical autoimmune disease diagnosis, antibody tests are of little predictive value. The study in around 17000 North Indian schools used EMA as the main screening tool followed by intestinal biopsy. Ventura et.al. showed that the long term undiagnosed and untreated celiac disease make it likely to cause autoimmunity to other organs. This can cause Type-

I diabetes, autoimmune thyroiditis, autoimmune alopecia, dermatitis herpetiformis, collagen diseases, and autoimmune Hepatitis.

9. Possible Clinical Manifestations of Celiac Disease

The manifestation of CD characterized into two categories one is typical symptoms and the other one is atypical symptoms. Typical symptoms include chronic diarrhoea, Failure to thrive. While atypical symptoms include Secondary to malabsorption, Hypochromic anemia, Short stature(height below the average height of peers), Bone loss, Recurrent abortions, Accumulation of fat in the liver, Recurrent abdominal pain, Independent of malabsorption, Dermatitis herpetiformis, Dental enamel hypoplasia, lack of voluntary coordination of muscle movements, Alopecia, Primary biliary cirrhosis, Isolated hypertransaminasemia, Recurrent aphthous stomatitis, Myasthenia gravis, recurrence of acute pericarditis symptoms, Psoriasis, Polyneuropathy, Epilepsy (with or without intracranial calcifications), Vasculitis, Dilatative cardiomyopathy, Hypo/hyperthyroidism and associated conditions includes Possibly gluten dependent, IDDM, Hashimoto's disease, Autoimmune hepatitis, Sjogren's syndrome, Addison disease, Autoimmune atrophic gastritis, Autoimmune emocytopenic diseases, Gluten independent, Down syndrome, Gonadal dysgenesis, Williams syndrome, Congenital heart defects, deficiency of IgA.

9.1. Chronic Diarrhea

In diarrhoea patients have increased stool frequency, loose stool or urgency of bowel movement these are key symptoms. In the case of chronic diarrhoea, symptoms last more than four weeks [25]. Patient with chronic diarrhoea is categorized into two different categories one is functional etiology and another one is organic etiology. When abdominal pain associated with diarrhoea it comes under functional etiology while the absence of abdominal pain comes under organic etiology [26].

9.2. Hypochromic Anemia

Hypochromic anemia is the condition in which red blood cells look paler than normal. Redness of cell decrease due to the reduction of hemoglobin content of RBC. Diagnosis of anemia can be done by measuring the concentration of Hemoglobin and hematocrit in a patient [27,28,29,30].

9.3. Short Stature

Various etiological conditions are responsible for Short stature and give rise to primary and secondary growth disorder [31]. The primary growth disorder includes clinically defined syndromes and they are intrinsic to the growth plate, these factors result in osteochondrodysplasias and they born small for gestational age. While secondary growth disorder relates to GH deficiency. The reported range is 1.3-19.8% among children's [32].

9.4. Bone Loss

Bones are highly metabolically energetic tissue. It undergoes remodelling throughout the life which includes bone formation and resorption processes. The imbalance between these two activity leads to bone loss [33].

9.5. Recurrent Abortions

It is also referred to pregnancy loss or miscarriage and defined as the loss of pregnancy or loss of fetus/embryo before 20 weeks and less than 400g of fetus weight [34].

9.6. Dental Enamel Hypoplasia

In dental enamel hypoplasia demarcating line surrounds the crown of the injured teeth occur due to extensive enamel distribution this is visible both radiographically and clinically. Mostly occurs in children's in the age of two years [35].

9.7. Alopecia

It refers to the loss of hair from part of the head and leads to psychological distress [36]. Half of the male after 50 years of age and a quarter of females are affected. The hair loss occurs due to male hormone or genetic factors or some time both are involved. Treatment involves either hair transplant surgery or minoxidil medication [37,38].

9.8. Recurrent Aphthous Stomatitis

The most common painful oral mucosal condition associated with mouth ulceration seen among the number of patients. It is characterised by recurring several bouts of solitary or shallow ulcers, at an interim of few days to few months [39].

9.9. Hashimoto's Disease

It is an autoimmune disorder and also known as Hashimoto's thyroiditis and Chronic lymphocytic thyroiditis involve gradual distortion of the thyroid gland. There are no early symptoms but after some time thyroid gland may large and form painless goitre.

9.10. Sjogren's Syndrome

It characterized as an autoimmune disorder which affects the moisture-producing gland of the body. Primary symptoms include dryness of eye and mouth.

9.11. Gonadal Dysgenesis

Disorder of the male and female reproductive system. It is characterized as replacement of reproductive tissues with less functional or fibrous tissue and defective development of embryo and gonads.

10. Dietary Chart for CD Person

A patient suffering from CD must follow strict dietary instructions to prevent further complications of the disease (Table 1).

Table 1. Dietary chart for CD patients

Diet may include	Not included in the diet
Bakery food includes	
Biscuits, Cookies, Cake, Bread burger, Pie pizza	Cakes and Biscuits made with Arrow root, Rice or Corn flour
Cereals	
Semolina, Vermicelli, Broken wheat, Noodles, Pasta, Wheat flour	Maize, Rice, Water chestnut, Barley
Sweets and Confectionary	
Chocolates, Toffees, Cewing gums, Ice-cream, Custard	Sugar candy, Homemade sweets, Ice cream, Jam
Beverages	
Flavored milk, Canned soups, Nutritional drinks	Fruit juices, Home made clear soups, Buttermilk, Coffee

11. Pathophysiology of CD

11.1. Gluten and Epithelial Transport of Peptide Fragments

The wheat, rye, and barley all belong to a tribe called Triticeae, but oats belonging to the tribe Aveneae (Figure 2). Although gluten is considered as a trigger of CD, mainly found in wheat. The gliadins and glutenins are the two main proteins found in gluten mainly involve in trigger [40,41,42]. The peptides hordeins and secalins are present in rye and barley respectively are also capable of activating disease. The gliadins, glutenins, secalins, and hordein have high contents of glutamines and pralines. Due to the presence of high content of pralines and glutamines, they show resistance toward the degradation by gastric acid, pancreatic, and brush-border enzymes because these are lacking in prolyl endopeptidase activity [44,45]. The peptide fragments transport across the small intestine and affects the permeability. This follows the transcellular pathway. However, it is unclear till now that either intestinal inflammation or altered permeability which one is the primary cause. The transcellular transport of gliadin, which involves the abnormal retro-transport of immunoglobulin A (IgA)-gliadin by the CD71 receptor (Cluster of Differentiation 71) [46]. The activation of CD71 receptor, escape the degradation of gliadin and translocation to the lamina propria.

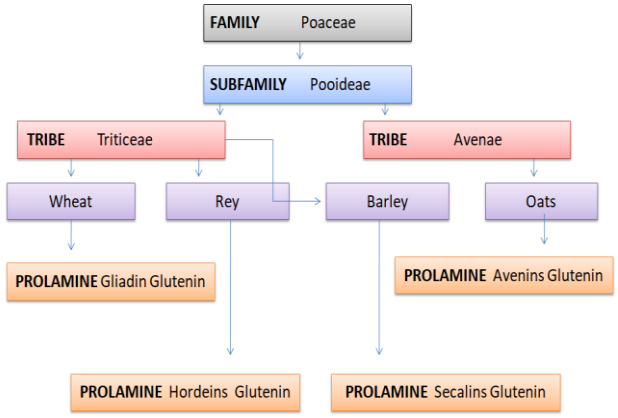

Figure 2. Family of grains

11.2. Microbiota

The microbiota is the micro-organism of a particular environment. A wide variety of complex micro-organism is found in the human intestine. The intestinal microbes are influenced by diet. The interaction between microbes and diet content affect metabolic functions. It will contribute to the number of phenotypic conditions like inflammatory bowel disease, obesity and CD [47]. In 2004, a study was performed on CD patients which revel that a rod shape bacteria was found in the intestine of CD patients [48]. There is a significant difference between gut microbiome samples of CD patients, first degree relatives and the non CD person [49]. Additional studies found that there is a difference in composition of faecal and mucosal content (Bacteroides, Clostridium, Bifidobacterium, Lactobacillus, Escherichia coli, and Staphylococcus) of CD and non CD patients [50]. The animal studies have suggested that the microbiome in CD may alter the intestinal permeability, therefore contribute to the pathogenesis of the disease [51].

12. Diagnosis

12.1. Anti-tissue Transglutaminase Antibodies

The enzyme-linked immunosorbent assay technique is used to detect IgA anti-tissue transglutaminase antibodies (tTGA) in the blood of CD patients [52,53]. While IgA anti-endomysial (IgA EMA) antibodies are employed as a confirmatory test in tTGA positive cases. This test shows greater sensitivity and accuracy in diagnosis.

12.2. Anti-gliadin Antibodies

This diagnostic procedure is no longer recommended due to its low specificity and selectivity, except in young children.

12.3. De-amidated Gliadin Peptides

This test is a replacement of Anti-gliadin antibodies, and involve immunoassay to deamidated gliadin peptides, IgA and IgG [54]. It provides more accurate and specific results.

12.4. Histology

It is considered as a gold standard for diagnosis of CD in adulthood, involves assessment of different entities: decreased enterocyte height, villous atrophy, inflammatory infiltrates in small-bowel mucosal biopsies. The endoscopy studies are performed to analyze intestinal biopsy samples of the patient [55].

12.5. In Vitro Gluten Challenge Test

The in vitro gluten challenge test was performed on duodenal mucosa using culture cells [56,57]. This provides information regarding gluten-sensitive immunological activation in celiac disease.

13. Treatment

13.1. Modified Grains

Small interfering RNA (siRNA) technology or selective wheat breeding strategies must be developed for modified grains production.

13.2. Life-long Gluten-free Diet

The lifelong gluten-free diet is advised to the CD patient. It provides recovery of mucosal damage and improvement of symptoms within a few weeks.

13.3. Gluten-degrading Enzymes

The bacterial prolyendopeptidase therapy accelerates the gluten digestion in the gastrointestinal tract and also helps in the distortion of T cell epitopes [58].

13.4. Rho/Rho Kinase Inhibition

The permeability of intestine depends on Rho kinase (ROCK) activity [59]. The inhibition of ROCK reverse the gluten-dependent and increase the permeability of the intestine.

14. Conclusion

As there is no cure of CD, preventive measures and diet need for the patients. There are numbers of diagnostic methods available which includes; Anti-tissue transglutaminase antibodies, Anti-gliadin antibodies, In vitro gluten challenge test, De-amidated gliadin peptides and Histology for the early diagnosis**.** *All the* diagnostic and treatment approaches including gluten-free diet plans are some measures which improve the quality of life.

References

[1] Thomas C. “On the coeliac affection. In: Major Classic descriptions of disease”. *Springfield, IL: Charles C. Thomas* 1945, 600-601.

[2] McDonald WC, Dobbins WO III, Rubin CE. “Studies of the familial nature of celiac sprue using biopsy of the small intestine”. *N Engl J Med*. 1965, 272: 448-456.

[3] Benecke R. Ueber die Spruekrankheit (Aphthae tropicae). Verh Dtsch Ges Pathol, 1910; 14: 132.

[4] Mawhinney H, Tomkin GH. “Gluten enteropathy associated with selective IgA deficiency”. *Lancet*, 1971, 2: 121-124.

[5] Howell MD, Austin RK, Kelleher D, Nepom GT, Kagnoff MF. “An HLA-D region restriction length polymorphism associated with celiac disease”. *J Exp Med*, 1986, 164: 333-339.

[6] Ferguson A, MacDonald TT, McClure JP, Holden RJ. “Cell-mediated immunity to gliadin within the small-intestinal mucosa in celiac disease”. *Lancet*, 1975, 1: 895-897.

[7] Cataldo F, Montalto G. “Celiac disease in the developing countries: a new and challenging public health problem”. *World J Gastroe, nterol*. 2007, 13: 2153-2159.

[8] Paulley JW, Fairweather FA, Leeming A. “Post-gastrectomy steatorrhoea and patchy jejunal atrophy”. *Lancet*, 1957, 272: 406-407.

[9] Taylor AK, Lebwohl B, Snyder CL, Green PHR. Celiac disease. In: Pagon RA, Adam MP, Ardinger HH. “*Gene Reviews”*. Seattle, WA: University of Washington; 2015.

[10] Allu é IP, Pedi átrica N. *Enfermedad cel úca presente y futuro*. Madrid, Espa ña:Ergon; 2013

[11] Lundin KE, Wijmenga C. “Coeliac disease and autoimmune disease-genetic overlap and screening”. *Nat Rev Gastroenterol H*epatol, 2015, 12 (9): 507-1

[12] Molina-Infante J, Santolaria S, Montoro M, Esteve M, Fern ández-Bañares F. “Non-celiac gluten sensitivity: a critical review of current evidence”. *Gastroenterol Hepatol*, 2014, 37 (6): 362-71.

[13] Ludvigsson JF, Leffler DA, Bai JC, Biagi F, Fasano A, Green PH, Hadjivassiliou M, Kaukinen K, Kelly CP, Leonard JN, Lundin KE, Murray JA, Sanders DS, Walker MM, Zingone F, Ciacci C. "The Oslo definitions for coeliac disease and related terms". *Gut (Review)*. 2013, 62 (1): 43-52.

[14] Zis P, Hadjivassiliou M. "Treatment of Neurological Manifestations of Gluten Sensitivity and Coeliac Disease". *Curr Treat Options Neurol (Review)*. 2019, 21 (3):10.

[15] Lu Shan, Øyvind Molberg, Isabelle Parrot, Felix Hausch, Ferda Filiz, Gary M. Gray, Ludvig M. Sollid, Chaitan Khosla. “Structural basis for gluten intolerance in celiac”. *sprue. Science*, 2002, 297: 2275-9.

[16] Heel DA, West J. “Recent advances in coeliac disease”. *Gut*, 2006; 55(7): 1037-46.

[17] Greco L, Romino R, Coto I, Di Cosmo N, Percopo S, Maglio M, Paparo F, Gasperi V, Limongelli MG, Cotichini R, D'Agate C, Tinto N, Sacchetti L, Tosi R, Stazi MA. “The first large population based twin study of coeliac disease”. *Gut*, 2002, 50: 624-8.

[18] Norris JM, Barriga K, Hoffenberg EJ, Taki I, Miao D, Haas JE, Emery LM, Sokol RJ, Erlich HA, Eisenbarth GS, Rewers M. “Risk of celiac disease autoimmunity and timing of gluten introduction in the diet of infants at increased risk of disease”. *JAMA*, 2005, 293:2343-51.

[19] Stene LC, Honeyman MC, Hoffenberg EJ, Haas JE, Sokol RJ, Emery L, Taki I, Norris JM, Erlich HA, Eisenbarth GS, Rewers M. “Rotavirus infection frequency and risk of celiac disease autoimmunity inearly childhood: a longitudinal study”. *Am J Gastroenterol*, 2006, 101:2333-40.

[20] Carolina Salazar, Jennyfer M Garc á-C árdenas and C ésar Paz-y-Mi ño. “Understanding Celiac Disease From Genetics to the Future Diagnostic Strategies”. *Clinical Medicine Insights: Gastroenterology*, 2017, Volume 10: 1-13.

[21] Seah PP, Fry LL, Rossiter MA, Hoffbrand AV, Holborow EJ. “Anti-reticulin antibodies in childhood celiac disease”. *Lancet*, 1971, 2: 681-682.

[22] Chorzelski TP, Sulej J, Tchorzewska H, Jablonska S, Beutner EH, Kumar V. “IgA class endomysium antibodies in dermatitis herpetiformis and coeliac disease”. *Ann N Y Acad Sci*, 1983, 420: 325-334.

[23] Ladinser B, Rossipal E, Pittschieler K. “Endomysium antibodies in coeliac disease: an improved method”. *Gut*, 1994, 35:776-778.

[24] Corrao G, Corazza GR, Andreani ML, Torchio P, Valentini RA, Galatola G, Quaglino D, Gasbarrin G, di Orio F. “CELIAC DISEASE PATHOGENESIS 241 screening of coeliac disease: choosing the optimal procedure according to various prevalence values”. *Gut*, 1994, 35: 771-775.

[25] Lawrence R. Schiller, Darrell S. Pardi and Joseph H. Sellin, Chronic Diarrhea: Diagnosis and Management, Clinical Gastroenterology and Hepatology 2016.

[26] Lacy BE, Mearin F, Chang L. “Bowel disorders. *Gastroenterology”*. 2016, 150:1393-1407.

[27] Gebreweld A, Bekele D, Tsegaye A. “Hematological profile of pregnant women at St. Paul's Hospital Millennium Medical College”. *Hematol*, 2018, 18:15.

[28] Needs T, Lynch DT. StatPearls [Internet]. StatPearls Publishing; Treasure Island (FL): Nov 23, 2018. Beta Thalassemia.

[29] Farashi S, Harteveld CL. “Molecular basis of α-thalassemia. Blood Cells Mol”. 2018, 70:43-53.

[30] Warner MJ, Kamran MT. StatPearls [Internet]. StatPearls Publishing; Treasure Island (FL): Nov 14, 2018. Anemia, Iron Deficiency.

[31] Oostdijk W, Grote FK, de Muinck Keizer-Schrama SM, Wit JM. “Diagnostic approach in children with short stature”. *Horm Res*, 2009; 72:206-17.

[32] Savage M.O, Backeljauw P.F, Calzada R, Cianfarani S, Dunkel L, Koledova E, Wit J.M, Yoo H.-W. “Early Detection, Referral, Investigation, and Diagnosis of Children with Growth Disorders”. *Horm Res Paediatr* 2016, 85:325-332.

[33] David J Hunter and Philip N Sambrook, Bone loss: Epidemiology of bone loss, Arthritis Res. 2000; 2(6): 441-445.

[34] Zegers-Hochschild F, Adamson GD, de Mouzon J. "International Committee for Monitoring Assisted Reproductive Technology; World Health Organization. International Committee for Monitoring Assisted Reproductive Technology (ICMART) and the World Health Organization (WHO) revised glossary of ART terminology". *Fertil Steril*, 2009, 92(5):1520-1524.

[35] Meera Sandhu, Shweta Gulia, Mehak Nagpal and Vinod Sachdev, Circular Enamel Hypoplasia: A Rare Enamel Developmental Disturbance in Permanent Teeth, J Clin Diagn Res. 2014 Aug; 8(8): ZD39-ZD40

[36] Nalluri, R; Harries, M. "Alopecia in general medicine". *Clinical Medicine*. 2016, 16 (1): 74-8.

[37] McElwee, K. J.; Shapiro, J. S. "Promising therapies for treating and/or preventing androgenic alopecia". *Skin Therapy Letter, 2012, 17 (6): 1-4.*

[38] *Leavitt, M. "*Understanding and Management of Female Pattern Alopecia*". Facial Plastic Surgery. 2008, 24 (4): 414-427.*

[39] Scully C, Porter S. Oral mucosal disease: Recurrent aphthous stomatitis. Br J Oral Maxillofac Surg. 2008; 46: 198-206.

[40] Van de Wal Y, Kooy YM, van Veelen P. "Glutenin is involved in the glutendriven mucosal T cell response". *Eur J Immunol*, 1999, 29: 3133-9.

[41] Molberg O, Solheim Flaete N, Jensen T. "Intestinal T-cell responses to highmolecular-weight glutenins in celiac disease". *Gastroenterology*, 2003, 125:337-44.

[42] Dewar DH, Amato M, Ellis HJ. "The toxicity of high molecular weight glutenin subunits of wheat to patients with coeliac disease". Eur *J Gastroenterol Hepatol*, 2006, 18:483-91.

[43] Vader LW, Stepniak DT, Bunnik EM. "Characterization of cereal toxicity for celiac disease patients based on protein homology in grains". *Gastroenterology*, 2003, 125:1105-13.

[44] Shan L, Molberg O, Parrot I. "Structural basis for gluten intolerance in celiac sprue". *Science*, 2002, 297:2275-9.

[45] Hausch F, Shan L, Santiago NA. "Intestinal digestive resistance of immunodominant gliadin peptides". *Am J Physiol Gastrointest Liver Physiol*, 2002, 283: G996-1003

[46] Matysiak-Budnik T, Moura IC, Arcos-Fajardo M. "Secretory IgA mediates retrotranscytosis of intact gliadin peptides via the transferrin receptor in celiac disease". *J Exp Med*, 2008, 205: 143-54.

[47] Muegge BD, Kuczynski J, Knights D. "Diet drives convergence in gut microbiome functions across mammalian phylogeny and within humans". *Science*, 2011, 332:970-4.

[48] Forsberg G, Fahlgren A, Horstedt P. "Presence of bacteria and innate immunity of intestinal epithelium in childhood celiac disease". *Am J Gastroenterol*, 2004, 99:894-904.

[49] Tjellstrom B, Stenhammar L, Hogberg L. "Gut microflora associated characteristics in first-degree relatives of children with celiac disease". *Scand J Gastroenterol*, 2007, 42: 1204-8.

[50] Sanchez E, Donat E, Ribes-Koninckx C. "Intestinal Bacteroides species associated with coeliac disease". *J Clin Pathol*, 2010, 63:1105-11.

[51] Cinova J, De Palma G, Stepankova R. "Role of intestinal bacteria in gliadininduced changes in intestinal mucosa": study in germ-free rats. PLoS One 2011; 6:e16169.

[52] Losowsky MS. "A history of coeliac disease". *Dig Dis*, 2008, 26: 112-120.

[53] Dicke WK, Weijers HA, Van de kamer JH. "Celiac disease. II. The presence in wheat of a factor having a deleterious effect in cases of coeliac disease". *Acta Paediatr*, 1953, 42: 34-42.

[54] Fasano A, Catassi C. "Current approaches to diagnosis and treatment of celiac disease: an evolving spectrum". *Gastroenterology*, 2001, 120: 636-651.

[55] Assimakopoulos SF, Papageorgiou I, Charonis A. "Enterocytes' tight junctions: From molecules to diseases". *World J Gastrointest Pathophysiol*, 2011, 2: 123-137

[56] Cataldo F, Montalto G. "Celiac disease in the developing countries: a new and challenging public health problem". *World J Gastroenterol*, 2007, 13: 2153-2159.

[57] Catassi C, Doloretta Macis M, Rätsch IM, De Virgiliis S, Cucca F. "The distribution of DQ genes in the Saharawi population provides only a partial explanation for the high celiac disease prevalence". *Tissue Antigens*, 2001, 58: 402-406.

[58] Trynka G, Wijmenga C, van Heel DA. "A genetic perspective on coeliac disease". *Trends Mol Med*, 2010, 16: 537-550.

[59] Romanos J, van Diemen CC, Nolte IM, Trynka G, Zhernakova A, Fu J, Bardella MT, Barisani D, McManus R, van Heel DA, Wijmenga C. "Analysis of HLA and non-HLA alleles can identify individuals at high risk for celiac disease". *Gastroenterology*, 2009; 137: 834-840, 840.e1-3.