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RESEARCH ARTICLE

CELIAC DISEASE AND ITS IMPACT ON AUTOIMMUNE THYROID

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Abstract

The small intestinal condition known as Celiac Disease (CD) or gluten-sensitive enteropathy is brought on by the body's immune system reacting to gluten consumption. In populations in the West, it is quite prevalent, with an incidence of 1%. Patients with autoimmune thyroid illness, type 1 diabetes mellitus, autoimmune liver diseases, and inflammatory bowel disease have been observed to have a higher prevalence of CD among autoimmune disorders. Autoimmune thyroid diseases are more common in persons with CD, with hypothyroidism being more common than hyperthyroidism. Examining the frequency of CD in patients with ATD was the goal of this investigation. Adopting a Gluten-Free Diet (GFD) promotes the development of related disorders and enhances the entire therapeutic course. Certain conditions, including iron deficiency anaemia, are made worse by the GFD and eventually go away. This makes it possible to better regulate diseases like type 1 diabetes mellitus. Adequate GFD compliance may also slow down the progression of various other problems and/or related disorders, particularly if started early.

Introduction:-

Gluten consumption causes Celiac disease (CD), a long-term immune-mediated condition that develops in people who are genetically prone to it. In genetically susceptible individuals, an immune-mediated enteropathy known as CD is triggered by the intake of gluten, a protein complex present in wheat and related cereals including barley, rye, and oats. CD is a common condition with a prevalence of approximately 1% in Western nations. However, it is incredibly neglected, partly because many individuals are asymptomatic and partly because of the misconception that CD is uncommon. Patients with specific abnormalities and autoimmune conditions, including Down syndrome, Turner syndrome, type 1 diabetes mellitus, and Autoimmune Thyroid Diseases (AITD), have reported experiencing it often. In children, gastrointestinal problems, apparent malabsorption, weight loss, and/or developmental delay are the most common presentations of CD. Adults who have elevated serum markers and histology are largely asymptomatic. Extraintestinal symptoms including amelogenesis imperfecta or herpetiform eczema are atypical characteristics of CD shown in Fig.1[1].

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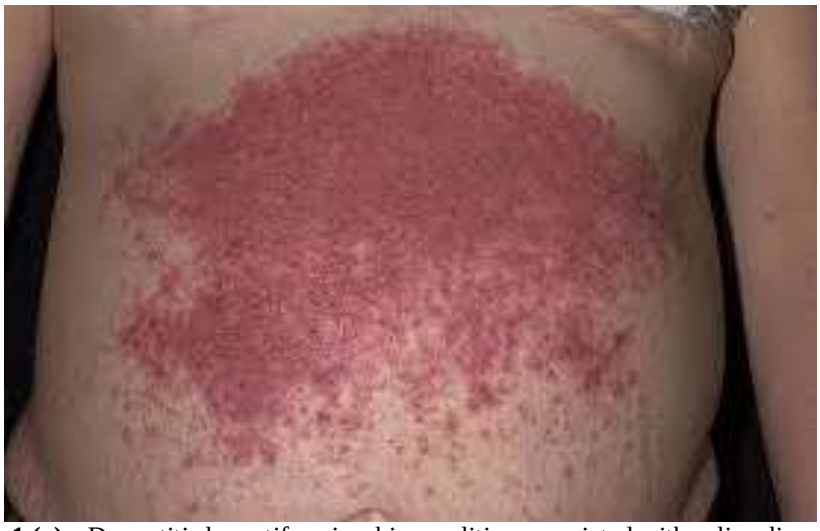

Fig.1 (a):- Dermatitis herpetiformis- skin condition associated with celiac disease.

Because CD is a chronic and silent disease, many cases are found through familial or random screening [2]. Highly accurate and precise serological assays such tissue transglutaminase, endomysial, and deamidated gliadin peptide antibodies have become increasingly important in the workup of celiac disease, even if small intestinal biopsies are still the gold standard for diagnosis. As of now, there is no cure for celiac disease other than a lifelong, rigorous gluten-free diet.

Dysfunction of the immune system is the cause of polygenic and multifactorial disorders known as autoimmune thyroid diseases [3]. The AITD is made up of Graves' disease (GD) and Hashimoto's thyroiditis (HT), both of which are marked by autoreactive B and T cells entering into the thyroid mucosa [4]. With a rate of 2% to 3% of the overall population, the probability of Hashimoto's thyroiditis is approximately 3.5 cases per 1000 persons per year in women and 0.8 cases per 1,000 in men. 1% to 2% of women and 0.1% to 0.2% of men have Graves' disease [5]. The main mechanism for tolerance breakdown and illness onset, according to epidemiological studies, is the interaction between genetic vulnerability and environmental triggers (such as infection, food, iodine, smoking, and alcohol) [6].

It has also been shown that chemokines and cytokines are involved in the pathophysiology of GD and HT. The two main antibodies associated with Hashimoto's disease are thyroid peroxidase and thyroglobulin. However, anti-TPO and anti-Tg antibodies are also present in 70% of patients with Graves' disease [7]. Similarly, thyroid-stimulating hormone receptor has been identified in a small percentage of patients with Hashimoto's disease, despite being the most prevalent autoantigen in Graves' disease. Thyrotoxicosis is typically the clinical manifestation of GD, whereas hypothyroidism is the characteristic of HT. External gluten-related aspects, such as age at first commencement, breastfeeding concurrently, length of gluten exposure, gluten-free diet, etc., do not provide substantial proof linking CD to AITD. This Review aims in finding the relationship between celiac disease and autoimmune thyroid.Table 1 depicts the AD associated with Celiac disease in terms of Liver diseases, Endocrine diseases, Rheumatological/connective tissue diseases.

Table 1:- AD associated with Celiac disease in terms of Liver diseases, Endocrine diseases, Rheumatological/connective tissue diseases.

Liver diseases	**Rheumatological/connective tissue diseases**
Primary biliary cirrhosis	Rheumatoid arthritis
Autoimmune hepatitis	uvenile rheumatoid arthritis/Juvenile idiopathic arthritis
Primary sclerosing hepatitis	Sjogren’s syndrome
Endocrine diseases	Systemic lupus erythematosus
Diabetes mellitus	Cardiological diseases
Autoimmune thyroid disease	Dilated cardiomyopathy
Addison’s disease	Autoimmune pericarditis

Gluten And Celiac Disease

A group of proteins used for storage present in wheat, barley, and rye grains is referred to as gluten [8]. Gluten is an inflammatory protein that can be found in wheat, barley, and other grains. Eating gluten can cause celiac disease. Other names for the illness include enteropathy caused by gluten, nontropical sprue, and celiac sprue. Proline and glutamine residues are common in gluten proteins. They are resistant to gastrointestinal digestion because of their high proline concentration. While the gluten proteins found in barley and rye are referred to as hordeins and secalins, accordingly, the gluten proteins found in grain are classified as gliadins and glutenins.Individuals diagnosed with CD increase their CD4+ T cell reaction to multiple different gluten peptides, which are identified in relation to CD-associated HLA-DQ proteins [8]. Furthermore, patients produce antibodies that are particular to gluten proteins.

When gluten is eliminated from the dietary habits, the gut ulcers in the majority of CD patients fully resolve and then return when the patients consume gluten. Because they alter with gluten exclusion or obstacle, the presence of autoantibodies specific for TG2 and the increased quantity of intraepithelial cytotoxic T lymphocytes are each influenced by gluten [9]. Gluten-reactive CD4+T lymphocytes with HLA-DQ2 or HLA-DQ8 restriction are present in the gastrointestinal mucosa of CD patients but not in normal individuals [10]. Owing to the robust HLA correlation, CD4+ T cells are most likely important for the progression of the illness. The overexpression of some interleukins, primarily of the IL-15 type, in conjunction with nonclassical MHC class I molecules in the epithelium is another important feature of CD. Although the CD4+ T cell response may play a part, it is not enough on its own to cause these changes in the intestinal epithelium. These findings support the theory that a natural factor that aids in the process of adaptation is usually present in conjunction with a robust immune system response [11].

Prevalence of clinical conditions of CD in autoimmune thyroid disease:

There is a higher frequency of CD among individuals with AITD, according to multiple screening studies, albeit estimates range widely. 1.6% of AITD patients had biopsy-confirmed CD, according to a systematic review of 27 studies. This prevalence was greater than that found in general population screening studies. Additionally, it was found that children with AITD had a higher prevalence of the CD (6.2%) than did adults (2.7%) [12]. Authors in [13] used a combination of biochemical testing for malabsorption, IgA-class reticulin and endomysium antibodies (EmA), IgA- and IgG-class gliadin antibody tests, and various other procedures to screen 83 patients with inflammatory thyroid disorders for celiac disease. Out of the 83 individuals, 3 had no symptoms and had a prior diagnosis of celiac disease, meaning that the overall incidence was 4.8%. The results showed that people with autoimmune thyroid illnesses had a higher frequency of subclinical CD [13].

Anti-gliadin and antiendomysial antibodies were seen in four of the 92 patients with autoimmune thyroid diseases (47 with chronic AITD, 22 with Hashimoto's thyroiditis, and 23 with Graves' disease) [14]. Five out of 150 newly diagnosed AITD patients (3.3%) had positive serum endomysial antibodies, according to a related study [25]. Six out of 172 patients with autoimmune thyroiditis tested positive for anti-endomysium in an examination program. Five of these individuals had intestinal biopsies, which demonstrated complete villous atrophy. In a different investigation, IgA anti-tTG was found in seven autoimmune thyroiditis patients, whereas IgA endomysial antibody was found in only six patients. A duodenal biopsy verified the diagnosis of CD, showing mild villous atrophy in one case and substantial villous atrophy in six. Remarkably, none of the euthyroid controls had any IgA antibodies found in them [26].

Authors in [27] found that 2% of individuals with autoimmune thyroid illness had celiac disease in a group study. Surprisingly, the serologic markers for these two celiac patients were insignificant six months after they started a gluten-free diet. In 91 paediatric AITD patients, 9.5% had celiac disease, according to retrospective research conducted in Italy. Furthermore, it was shown that three (6.1%) of these kids had first- or second-degree relatives who had CD. Using the IgA anti-tTG antibody and total serum IgA, 103 healthy kids and 101 kids with AITD were assessed for CD. None of the serum samples from healthy children tested positive for IgA anti-tTG antibody, whereas eight children with AITD (7.9%) showed positive for the immunological indicators. Additionally, an intestinal biopsy revealed subtotal villous atrophy in five individuals [28]. Two out of 66 individuals with AITD who were enrolled in comparable research also included female teenagers were found to have CD [29]. 914 AITD patients were enrolled in cross-sectional research. 117 of them tested positive for celiac disease (12.8%). Of the 87 seropositive people who had duodenal biopsies, about 39 (44.8%) had positive histology results for celiac disease.

Effect Of Gluten-Free Diet On Aitd

A genetically engineered pathway between gut and thyroid tissue transglutaminase seems to be the basis for the strongest link between gluten ingestion and thyroid damage [30]. Many research has examined the impact of a gluten-free diet on thyroid illness in individuals who also have CD, but less is known about how a GFD may affect AITDs in people who do not have CD or celiac-related antibodies. A GFD may be able to correct thyroid problems in certain individuals, according to an Italian multidisciplinary study that examined the thyroid function of 128 newly diagnosed CD patients before and one year after the GFD was implemented [31].

Authors in [32] stated that the symptoms associated with hypothyroidism and thyroxine dosage alleviated in three AITD patients who had concurrent CD who adhered to a GFD for six months. Nevertheless, following an 18-month monitoring, the anti-Tg and anti-TPO antibody levels changed in only one patient. In a placebo-controlled study [33], drug-naive women with HT were compared to see no dietary intervention (n = 18) or six months on a GFD (n = 16). Thyroid enzyme and thyroglobulin antigens were decreased, 25-hydroxy vitamin D was elevated, and the structural parameter inference approach-gain of thyroid index was enhanced by the GFD. These changes were connected with variations in antibody levels. The levels of free triiodothyronine and thyrotropin were unaffected.

A current study on the amount of TPO antibodies found in 10 newly diagnosed patients with CD over the course of a year revealed that a gluten-free diet did not appear to stop the process of autoimmune disease from progressing [34]. Moreover, the thyroid volume dropped considerably (5.6 cm3 versus the starting 6.4 cm3) when compared to the patient group without CD, suggesting that thyroiditis persisted even after a GFD was put in place. Six months after starting an AITD patient with CD on a gluten-free diet, Mainardi et al. saw a remarkable clinical recovery of CD, carry out modification of the villous anomalies and disappearance of all three serum celiac markers; however, an unanticipated and gradually rising in the anti-thyroid antigens titer was noticed [35].

Authors in [36]. made several intriguing discoveries in comprehensive research. Patients with both HT and CD were shown to require more T4, however a GFD could prevent this impact. In patients with HT and CD who were not following GFD, the therapeutic dose of T4 needed to be increased by about 50% in order to reach the target TSH levels. In light of the aforementioned research, it stands to reason that diagnosing and treating CD enhances drug absorption for illnesses like HT. An experimental trial by authors in [36] found that a year of gluten avoidance improved 28.6% of individuals' thyroiditis due to autoimmune disease. However, the researchers did note that when new cases of anti-thyroid antibody positivity appeared, GFD adherence had no bearing on the presence of antibodies.

Conclusions:-

Main goal of this article is to compile the most pertinent research between autoimmune thyroid and its impact on celiac disease. Genetically, there seems to be a large overlap between CD and AITD. AITD patients should be routinely evaluated for CD autoantibodies as part of a continuous approach. This would provide accurate information about the frequency of co-occurrence and the temporal sequence of events in each patient. There is ample evidence of the increasing frequency of CD in AITD patients. Additionally, the bulk of research on the benefits of a gluten-free diet in managing both AITD and concurrent CD in patients has demonstrated its favourable effects. While people with AITD should be regarded as highly susceptible to CD, there is disagreement on the necessity of frequent screening because it is not very cost-effective and there haven't been many cases from earlier screening efforts. Moreover, it is difficult to recognize the simultaneous development of both of these conditions early on due to the prevalence of preclinical appearances of AITD and CD. In order to guarantee that patients with simultaneous AITD and CD receive the best care possible, a multidisciplinary approach is advised and should be integrated into the diagnostic algorithm of autoimmune thyroid illnesses due to the multisystemic character of CD.

References:-

[1] Dong YH, Fu DG: Autoimmune thyroid disease: mechanism, genetics and current knowledge, Eur Rev Med Pharmacol Sci. 2014, 18:3611-8

[2] Pharmacol Sci. 2014, 18:3611-8. 5. Diamanti A, Capriati T, Bizzarri C, et al.: Autoimmune diseases and celiac disease which came first: genotype or gluten?. Expert Rev Clin Immunol. 2016, 12:67-77.

[3] Lorini R, Larizza D, Scotta MS, Severi F: HLA in Graves' disease coexistent with coeliac disease. Eur J Pediatr. 1986, 145:241

[4] King AL, Moodie SJ, Fraser JS, Curtis D, Reid E, Dearlove AM, Ciclitira PJ: Coeliac disease: investigation of
[5] proposed causal variants in the CTLA4 gene region. Eur J Immunogenet. 2003, 30:427-32. 10.1111/j.1365-2370.2003.00430.x
[6] Valentino R, Savastano S, Maglio M, et al.: Markers of potential coeliac disease in patients with Hashimoto's thyroiditis. Eur J Endocrinol. 2002, 146:479-83. 10.1530/eje.0.1460479
[7] Mormile R: Celiac disease and Hashimoto's thyroiditis: a shared plot? . Int J Colorectal Dis. 2016, 31:947.
[8] Roy A, Laszkowska M, Sundström J, Lebwohl B, Green PH, Kämpe O, Ludvigsson JF: Prevalence of celiac disease in patients with autoimmune thyroid disease: a meta-analysis. Thyroid. 2016, 26:880-90.
[9] Cuoco L, Certo M, Jorizzo RA, et al.: Prevalence and early diagnosis of coeliac disease in autoimmune thyroid disorders. Ital J Gastroenterol Hepatol. 1999, 31:283-7.
[10] Valentino R, Savastano S, Tommaselli AP, et al.: Prevalence of coeliac disease in patients with thyroid autoimmunity. Horm Res Paediatr. 1999, 51:124-7. 10.1159/000023344
[11] Berti I, Trevisiol C, Tommasini A, et al.: Usefulness of screening program for celiac disease in autoimmune thyroiditis. Dig Dis Sci. 2000, 45:403-6. 10.1023/a:1005441400107
[12] Volta U, Ravaglia G, Granito A, et al.: Coeliac disease in patients with autoimmune thyroiditis, Digestion. 2001, 64:61-5. 10.1159/000048840
[13] Larizza D, Calcaterra V, De Giacomo C, et al.: Celiac disease in children with autoimmune thyroid disease . J Pediatr. 2001, 139:738-40. 10.1067/mpd.2001.118189
[14] Meloni GF, Tomasi PA, Bertoncelli A, Fanciulli G, Delitala G, Meloni T: Prevalence of silent celiac disease in patients with autoimmune thyroiditis from Northern Sardinia. J Endocrinol Invest. 2001, 24:298-302.
[15] Mainardi E, Montanelli A, Dotti M, Nano R, Moscato G: Thyroid-related autoantibodies and celiac disease: a role for a gluten-free diet?. J Clin Gastroenterol. 2002, 35:245-8. 10.1097/00004836-200209000-00009
[16] De Martino L, Di Donato I, Alfano S, D'Acunzo I, Di Pinto R, Capalbo D, Salerno M 2014: Prevalence of additional autoimmune diseases in autoimmune's thyroiditis children and their first-and second-degree relatives: results from a large, single center study. Horm Res Paediatr. 2014, 82:460.
[17] Sari S, Yesilkaya E, Egritas O, Bideci A, Dalgic B: Prevalence of celiac disease in Turkish children with autoimmune thyroiditis. Dig Dis Sci. 2009, 54:830-2. 10.1007/s10620-008-0437-1
[18] Sahin Y, Evliyaoglu O, Erkan T, Cokugras FC, Ercan O, Kutlu T: The frequency of celiac disease in children with autoimmune thyroiditis. Acta Gastroenterol Belg. 2018, 81:5-8.
[19] Farahid OH, Khawaja N, Shennak MM, Batieha A, El-Khateeb M, Ajlouni K 2014: Prevalence of coeliac disease among adult patients with autoimmune hypothyroidism in Jordan. East Mediterr Health J. 2014, 20:51-5.
[20] Marwaha RK, Garg MK, Tandon N, et al.: Glutamic acid decarboxylase (anti-GAD) & tissue transglutaminase (anti-TTG) antibodies in patients with thyroid autoimmunity. Indian J Med Res. 2013, 137:82-6.
[21] Teixeira LM, Nisihara R, Utiyama SR, Bem RS, Marcatto C, Bertolazo M, Carvalho GA: Screening of celiac disease in patients with autoimmune thyroid disease from Southern Brazil. Arq Bras Endocrinol Metabol. 2014, 58:625-9. 10.1590/0004-2730000003003
[22] Ch'ng CL, Biswas M, Benton A, Jones MK, Kingham JG: Prospective screening for coeliac disease in patients with Graves' hyperthyroidism using anti-gliadin and tissue transglutaminase antibodies. Clin Endocrinol. 2005, 62:303-6.
[23] Marwaha RK, Garg MK, Tandon N, et al.: Glutamic acid decarboxylase (anti-GAD) & tissue transglutaminase (anti-TTG) antibodies in patients with thyroid autoimmunity. Indian J Med Res. 2013, 137:82-6.
[24] Teixeira LM, Nisihara R, Utiyama SR, Bem RS, Marcatto C, Bertolazo M, Carvalho GA: Screening of celiac disease in patients with autoimmune thyroid disease from Southern Brazil. Arq Bras Endocrinol Metabol. 2014, 58:625-9. 10.1590/0004-2730000003003
[25] Ch'ng CL, Biswas M, Benton A, Jones MK, Kingham JG: Prospective screening for coeliac disease in patients with Graves' hyperthyroidism using anti-gliadin and tissue transglutaminase antibodies. Clin Endocrinol. 2005, 62:303-6.
[26] Mehrdad M, Mansour-Ghanaei F, Mohammadi F, Joukar F, Dodangeh S, Mansour-Ghanaei R. Frequency of celiac disease in patients with hypothyroidism. J Thyroid Res (2012) 2012:201538. doi: 10.1155/2012/201538
[27] Volta U, Caio G, Stanghellini V, De Giorgio R. The changing clinical profile of celiac disease: a 15-year experience (1998-2012) in an Italian referral center. BMC Gastroenterol (2014) 14:194.

[28] Losurdo G, Piscitelli D, Giangaspero A, Principi M, Buffelli F, Giorgio F, et al. Evolution of nonspecific duodenal lymphocytosis over 2 years of follow-up. World J Gastroenterol (2015) 21(24):7545–52.
[29] Ashok T, Patni N, Fatima M, Lamis A, Siddiqui SW. Celiac disease and autoimmune thyroid disease: the two peas in a pod. Cureus (2022) 14(6):e26243. doi: 10.7759/cureus.26243\
[30] Kahaly GJ, Frommer L, Schuppan D. Celiac disease and endocrine autoimmunity - the genetic link. Autoimmun Rev (2018) 17(12):1169–75.
[31] Passali M, Josefsen K, Frederiksen JL, Antvorskov JC. Current evidence on the efficacy of gluten-free diets in multiple sclerosis, psoriasis, type 1 diabetes and autoimmune thyroid diseases. Nutrients (2020) 12(8):2316.
[32] Haupt-Jorgensen M, Groule V, Reibel J, Buschard K, Pedersen AML. Gluten-free diet modulates inflammation in salivary glands and pancreatic islets. Oral Dis (2022) 28(3):639–47.
[33] Hinks LJ, Inwards KD, Lloyd B, Clayton BE. Body content of selenium in coeliac disease. Br Med J (Clin Res Ed) (1984) 288(6434):1862–3.
[34] Chaudhary S, Dutta D, Kumar M, Saha S, Mondal SA, Kumar A, et al. Vitamin D supplementation reduces thyroid peroxidase antibody levels in patients with autoimmune thyroid disease: An open-labeled randomized controlled trial. Indian J Endocrinol Metab (2016) 20(3):391–8.
[35] Krysiak R, Kowalcze K, Okopień B. Gluten-free diet attenuates the impact of exogenous vitamin D on thyroid autoimmunity in young women with autoimmune thyroiditis: a pilot study. Scand J Clin Lab Invest (2022) 82(7-8):518–24.
[36] Krysiak R, Szkróbka W, Okopień B. The effect of gluten-free diet on thyroid autoimmunity in drug-naïve women with hashimoto's thyroiditis: A pilot study. Exp Clin Endocrinol Diabetes (2019) 127(7):417–22.