DOI: https://doi.org/10.53555/nnmhs.v8i5.1283 Publication URL: https://nnpub.org/index.php/MHS/article/view/1283

ASSOCIATION OF CELIAC DISEASE IN PATIENTS WITH TYPE 1.5 DIABETES MELLITUS: LITERATUR REVIEW

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ABSTRACT

Background: *Celiac disease (CD) and type 1 diabetes are immune-mediated diseases that share common susceptibility factors, primarily HLA genetics.* ***Objective and methods:*** *This systematic review and meta-analysis sought data from Cochrane, PubMed, Googlescholar, and other journal databases. We searched for the keywords "celiac disease" and "diabetes melitus". The inclusion criteria of the research to be included are research that examines the association of celiac disease in patients with type 1.5 diabetes melitus or latent autoimmune diabetes in adults (LADA), research subjects are adults (not animal), and use primary data.* ***Result:*** *All the studies found showed a close association between celiac disease and LADA or T1.5DM.* ***Conclusion:*** *LADA or type 1.5 DM and CD are autoimmune conditions that can coexist. HLA is a gene that plays a role in both diseases. Clear common risk factors, genetics and environment are likely to play an important role in the initiation of the condition.*

Keywords: *Celiac disease, Diabetes, Autoimmunity, LADA/T1.5DM*

INTRODUCTION

Diabetes mellitus (DM) is a group of metabolic diseases characterized by hyperglycemia resulting from impaired insulin secretion, insulin action, or both. Chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of various glands, especially the eyes, kidneys, nerves, heart, and blood vessels.[1]

The prevalence of DM is difficult to determine because the standard for establishing the diagnosis is different. According to the 2012 American Diabetes Association (ADA 2012) criteria, about 10.2 million people in the United States have diabetes. Meanwhile, in Indonesia the prevalence of DM is 1.5-2.3% of the population aged >15 years, even in the Manado area the prevalence of DM is 6.1%. The incidence of type 2 diabetes is higher in women than men.[2]

Type 1.5 DM, also known as latent autoimmune diabetes in adults (LADA) is a slowly progressing autoimmune diabetes characterized by T1DM-associated autoantibodies and a presentation at diagnosis similar to that of T2DM patients.[3] Celiac disease (CD) and type 1 diabetes are immune-mediated diseases that share common susceptibility factors, primarily HLA genetics.[4]

Celiac disease (CD) is a chronicimmune-mediated enteropathy-precipitated by to dietary gluten in genetically predisposed individuals. Current diagnosis is based on demonstrating the enteropathy in small intestinal biopsies where histologic examination shows villous atrophy, crypt hyperplasia and intraepithelial lymphocytosis, and the presence of circulating CD-specific antibodies to tissue transglutaminase (tTG), deamidated gliadin peptides (DGP), and endomysium (EMA).[5]

Both have an increasing incidence worldwide indicating that, apart from genetic factors, environmental factors also play an important role in disease pathogenesis. Emerging evidence suggests that factors such as the gut microbiome and infectious agents modulate innate and adaptive immunity to increase the risk of CD and T1DM.[4]

This statistics is also debatable, as Finland has a high prevalence rate of both T1DM (>40/100,000) and CD (>39/100,000); therefore, this may just be a gross underestimation, as it comes from a study dated back to 1996. Recently high frequencies have been reported from populations that have wheat or barley as their staple crop. These include Oran (Algeria) as described above, North India (11.1.%), and Libya (10.3%).[6]

The recent reports from other populations that are not mainly wheat consuming, but also have higher prevalence rate are Saudi Arabia (11.3%), Denmark (10.4%), Sweden (9.67%), Canada (7.7%), Italy (6.65%), and Iran (6.2%). However, comparatively lower rates have been reported from Australia (5.7%), Tunisia (5.3%), Austria (5%), United Kingdom (4.42%), and Egypt (4%).[6]

The prevalence of CD in T1DM patients is 5–7 times more than the general population. Four to nine percent of the T1DM patients have been described to have CD, compared to the incidence of 1% in general population. However, this range is much broader as lowest incidence rates of 2.4% have been described in Finland and highest rate of 16.4% has been reported from Algeria.[6] This study looked at the association between celiac disease and type 1.5 diabetes mellitus or LADA.

METHODS

This study is a systematic review and meta-analysis. The source of this research data comes from literature obtained through the internet in the form of research results published on the internet, both in Cochrane, PubMed, Googlescholar, and other journal databases. We searched for the keywords “celiac disease” and “Type 1,5 Diabetes Melitus”.
The study included in this article is a study that focuses on the factors associated with celiac disease in DM. The inclusion criteria of the research to be included are research that examines the factors associated with celiac disease in DM, research subjects are adults (not animal studies), and use primary data. The purpose of this study was to see the relationship between blood glucose levels and the prognosis of COVID-19.

RESULT

The search results in the Pubmed journal database, we only found one journal that discussed the association of celiac disease in patients with type 1.5 diabetes mellitus. A Google scholar search shows three studies that are relevant to this study. Information on all the studies involved in this systematic review can be seen in Table 1.

Table 1. Search results

Author	Country	Method	Sample	Population	Period	Outcame
Sanchez et al (2007)[7]	Cuba	Retrospective study	142 respondent	Patients with LADA and T2DM	May 2005-May 2006	There was no difference between the frequency of CD-associated antibodies between LADA and T2DM subjects. The finding of CD-associated antibodies is more common in

						patients with normal or low BMI.
Kylokas et al (2016)[8]	Finland	Retrospective study	1358 respondent	Patient with CD, age at diagnosis ≥16 years	All patients prior to the study	Type 1 diabetes was markedly overrepresented in celiac disease, especially in men, whereas the prevalence of type 2 diabetes was comparable with the population. Concomitant type 1 or type 2 diabetes predisposes celiac patients to severe co-morbidities and type 1 diabetes also to poor dietary adherence.
Oujama et al (2019)[9]	Morrocco	Multicenter cross-sectional	276 respondent	Diabetic patients in children and adult	2016-2018	The current study provides evidence of a high prevalence of CD-specific autoantibodies in the T1D population. The coexistence of these two conditions is associated with poor glycemic control, lower height, and other autoimmune diseases. These findings may suggest the need for systematic screening of CD in T1D patients.

DISCUSSION

Celiac disease is a polygenic systemic immune-mediated enteropathy triggered by dietary gluten characterized by a specific serum antibody response. Celiac disease only involves the mucosa of the small bowel. The villi may be absent or atrophic and the crypt hyperplasia is present. This is similar to T1DM which is characterized by antibody-mediated destruction of pancreatic islet beta cells, so that blood glucose levels can no longer be maintained within the physiological range without exogenous insulin.[4]

Celiac disease and type 1 diabetes are both autoimmune diseases and associated with HLA-DQ2 and HLA-DQ8 genetic haplotypes. Of the 2.1 million people who have type 1 diabetes, approximately 8% to 10% have celiac disease. Type 1 diabetes presents with the classical symptoms of polydipsia and polyuria, whereas the diagnosis of celiac disease appears to need a high index of supposition since the symptoms are not as readily detectable.[10]

Both T1D and CD are inherited complex diseases with strong genetic components notably HLA. Recent genome wide association studies (GWAS) have identified single nucleotide polymorphisms (SNPs) associated with autoimmune conditions including T1D and CD. Overlap of genetic variants between T1D and CD (including HLA and non-HLA) underscores common pathogenic mechanisms and likely explains increased prevalence of concomitant disease.[4]

HLA, also known as the major histocompatibility complex (MHC), is involved in antigen presentation to T cells. The HLA region is the most polymorphic observed in the human genome with thousands of unique allele sequences. The MHC class II DQ peptides are associated with both CD and T1D, while MHC class I loci have also been shown to affect T1D susceptibility but not CD.[4]

HLA-DQ2 (also known as the haplotype DR3-DQ2) is found in about 90% of CD and 55% of T1D patients, while HLA-DQ8 is found in about 10% of CD and 70% of T1D patients. In clinical support of the HLA associations, approximately 33% of HLA-DQ2 homozygous individuals with T1D express tTG autoantibodies, compared to less than 2% of the T1D patients who lacked DQ2 and DQ8 genotypes.[4]

Thus, screening and reporting of celiac disease should be considered. This article addresses an overview of type 1 diabetes, celiac disease, their common genetic strand, possible reasons as to why celiac disease is underreported, and the challenges families face.[10]

The association between type 1 diabetes mellitus and celiac disease was first discovered in the 1960s. The estimated prevalence of celiac disease in patients with type 1 diabetes is about 6%, and about 1% in the general population. The significantly higher prevalence of celiac disease in diabetic patients led doctors to recommend CD screening after a diagnosis of type 1 diabetes, as well as celiac disease patients who were screened for type 1 diabetes.[11]

Both T1DM and CD are marked by the selective destruction of β cells of islets and enterocytes respectively. The triggering factor for the cascade of events is not known in T1DM, but the triggering factor is wheat gluten in CD. Because the causing factor in well known in CD, the pathogenic mechanisms of CD are far more precisely known compared to the mechanisms of T1DM.[3,6]

However, other than gluten, different infectious agents like viruses (adenovirus type 12, hepatitis C virus, rotavirus) have also been implicated as the risk factors for CD. This is evident from the fact that not all individuals who carry the genetic risk factors develop CD. Similarly, viruses such as enteroviruses and herpesviruses have also been described as the triggering factors for T1DM.[3,6]

There is no definite link between type 2 diabetes and celiac disease. Type 2 diabetes does have a genetic component, but they are not linked to the CD gene like type 1 diabetes. Overweight CD patients are common, with 40% of patients with CD being overweight at the time of diagnosis and 13% being obese. Many processed gluten-free products have an increased glycemic index with lower increases in fat and protein compared to gluten-containing foods.[11]

Sanchez (2007) showed that CD was not associated with pancreatic autoimmunity in patients with T2DM. Celiac disease causes a reduction in BMI in diabetes, whereas the autoimmunity of the pancreatic islets in these entities masks this effect. Other studies have shown that those with T1DM are more likely to develop CD than T2DM. LADA predisposes to worse CD, whereas T1DM decreases adherence to a gluten-free diet. The overall prevalence of T1DM in CD patients >30 years of age was 3.8%.[8]

The current study provides evidence of a high prevalence of CD-specific autoantibodies in the T1D population. The coexistence of these two conditions is associated with poor glycemic control, lower height, and other autoimmune diseases. These findings may suggest the need for systematic screening of CD in T1D patients.[9]

Symptoms and signs of CD can become apparent at any age into adulthood. CD patients (with or without concomitant T1D) have classic symptoms such as diarrhea, bloating, weight loss, and growth failure (in children). Celiac disease can also present with non-classical or asymptomatic symptoms. Non-classical and extra-intestinal bowel symptoms include constipation, heartburn, neuropathy and ataxia.[6]

The common symptoms are lethargy and diarrhea hence the name celiac sprue. Other gastrointestinal symptoms are abdominal distension, discomfort or pain, vomiting, and constipation. In childhood, failure to thrive is an important aspect of the history, while in adulthood the corresponding symptom would be unexplained weight loss.[3,12]

Symptoms from other than gastrointestinal systems include recurrent aphthous ulcers in the mouth, iron deficiency anemia, ataxia, chronic headaches, and delayed menarche. The incidence of some obstetric complications such as preterm labor, growth restriction, and stillbirth in women with the untreated celiac disease is higher.[3,12]

Clinical signs of CD include iron deficiency anemia or low bone density with or without accompanying symptoms. Individuals with subclinical disease, known as silent CD, are seropositive patients without gastrointestinal or extra-intestinal manifestations. The majority of CD patients with T1DM do not present with classic CD signs or symptoms. They may present with milder gastrointestinal symptoms than diabetic patients without CD.[6]

Researchers showed significant differences regarding the following clinical findings: pallor, chronic constipation, abdominal pain, bloating, and recent weight loss. This finding is comparable to that of Hansen et al.[13] who showed significant differences between 33 CD-T1D patients compared with 236 T1D alone, regarding abdominal pain, bowel movements and/or frequent bowel movements, bloating, constipation, arthralgia, fatigue, and frequent hypoglycemia, whereas no differences were reported about other symptoms, such as aphthous ulcers and tooth enamel damage.[9]

On another side, the impact of CD on growth in diabetic patients as well as the potential benefit of the gluten-free diet (GFD) on this parameter is still controversial. About that, Hansen et al.[13] found that at the time of CD diagnosis, CD-T1D patients had a smaller mean weight SD than T1D patients. Other authors reported similar results for weight SD and height SD. Our study showed a significant difference between the two groups in only height SD.

The recommendations for treatment of LADA with CD are the same as for all patients with CD. A strict GFD should be initiated in those with serological and histological evidence of CD. Patients should meet with a dietician for GFD teaching and should initiate a daily multivitamin given lack of certain vitamins and minerals in the GFD.[14] Most symptomatic patients will improve in 2-4 weeks on the GFD, although a portion of patients have persistent symptoms after 3-6 months referred to as non-responsive CD. Serologies should be checked after 3-4 months and then yearly when normalized.[15]

In patients with both LADA and CD, dietary compliance can be challenging. Indeed, adherence to the GFD among CD patients with diabetes ranges from 25-78%. Moreover, quality of life may be lower in patients with both diagnoses. A

recent study assessed quality of life in patients diagnosed with both LADA and CD and found lower scores than in matched patients with LADA alone, especially in respect to social functioning and general health perception.[4]

Treatment of CD may influence the course of LADA. LADA patients with undiagnosed CD show increased risk of diabetic retinopathy and nephropathy, although this has not been found in all studies. One study found that LADA with untreated CD had lower body mass index (BMI) and lower HbA1c scores compared to those without CD, although other studies have not found differences in BMI or glycemic control between diabetes with and without CD.[4]

Poorly controlled CD and subsequent weight loss may improve glucose control while adherence to a GFD in CD might improve nutritional absorption and thereby increase insulin requirements. However, diminished absorption of nutrients in untreated CD may increase the risk of hypoglycemia in patients with diabetes.[4]

Overall, it appears that following a GFD may be beneficial (or at least not harmful) in diabetes with CD; however, there is substantial heterogeneity in the literature.[4] The prognosis for patients with the correct diagnosis and treatment is good. Unfortunately, compliance with a gluten-free diet is very difficult and relapses are common. Some patients do not respond to a gluten-free diet or corticosteroids; they have a poor quality of life.[7]

CONCLUSION

LADa or type 1.5 DM and CD are autoimmune conditions that can coexist. HLA is a gene that plays a role in both diseases. Clear common risk factors, genetics and environment are likely to play an important role in the initiation of the condition.

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