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A Shared Path: Co-occurrence and Clinical Implications of Celiac Disease and Type 1 Diabetes Mellitus

Wojciech Florczak

Medical University of Lublin: Lublin, Poland

https://orcid.org/0009-0006-8003-0999

florczak.wojciech99@gmail.com

Joanna Śnieżna

Medical University of Lublin: Lublin, Poland

https://orcid.org/0009-0006-2713-0835

asia.sniezna@gmail.com

Jakub Dziewic

Medical University of Lublin: Lublin, Poland

https://orcid.org/0009-0008-4338-4573

dziewicjakub@gmail.com

Karol Dzwonnik
Medical University of Lublin: Lublin, Poland
https://orcid.org/0009-0007-1366-3945
karol.dzwonnik@gmail.com

Wiktoria Domino
Clinical Provincial Hospital No. 2 in Rzeszów, Poland
Lwowska 60, 35-501 Rzeszów, Poland
https://orcid.org/0009-0005-0034-7463
wiktoriadomino1604@gmail.com

Urszula Zelik
University Teaching Hospital them F. Chopin in Rzeszów, Poland
Fryderyka Szopena 2, 35-055 Rzeszów, Poland
https://orcid.org/0009-0009-3369-7936
ulazelik@gmail.com

Gabriela Trestka
Clinical Provincial Hospital No. 2 in Rzeszów, Poland
Lwowska 60, 35-501 Rzeszów, Poland
https://orcid.org/0009-0009-9504-8923
gabixtre@gmail.com

Maria Przygoda
Specialist Hospital named after Stefan Żeromski,
Independent Public Healthcare Facility (SP ZOZ), in Kraków
https://orcid.org/0000-0002-6409-7265
maria.przygoda@interia.pl

Jagienka Włodyka
University Teaching Hospital them F. Chopin in Rzeszów, Poland
Fryderyka Szopena 2, 35-055 Rzeszów, Poland

https://orcid.org/0009-0000-7243-7023
jagienka.wlodyka@gmail.com
Kamila Stępień
Independent Public Health Care Facility
of the Ministry of Internal Affairs and Administration in Kielce, Poland
Wojska Polskiego 51, 25-375 Kielce, Poland
https://orcid.org/0009-0000-3579-9308
kamila_stepien@onet.pl

Sabina Adamczyk
Independent Public Healthcare Facility
of the Ministry of Internal Affairs and Administration in Opole, Poland
https://orcid.org/0009-0003-9671-6619
adamczyksabinaa@gmail.com

ABSTRACT

Introduction:

Celiac disease (CeD) and Type 1 diabetes mellitus (T1DM) are autoimmune diseases that sometimes co-occur in genetically predisposed people. Both diseases share common genetic factors, such as human leukocyte antigens: HLA-DQ2 and HLA-DQ8. Apart from that, they share environmental factors such as gluten exposure, viral infections, and alterations in gut microbiota composition. CeD is a gluten-induced disease resulting in inflammation and impaired absorption of the nutrients, leading to malnutrition. In T1DM, β-cells in the pancreatic tissue are destroyed during the T-cell mediated reaction, which leads to impaired insulin production and development of insulin deficiency which leads to hyperglycemia and chronic complications.

Materials and methods:

This study is based on a review of multiple articles and prospective studies we managed to find online in the PubMed database.

Aim of the study:

The aim of the study is to investigate the clinical implications of T1DM and CeD, focusing on the importance of early screening for CeD in patients with T1DM and evaluate the challenges

in the management of both diseases simultaneously. Additionally, the study highlights the potential benefits of a personalized approach to treatment.

Conclusions:

The co-occurrence of CeD and T1DM is common and it's determined by shared genetic, immune, and environmental factors. Early screening and diagnosis are very important regarding the management strategies for these conditions. Gluten free diet (GFD) is the main treatment for CeD, but its adherence may be challenging, especially in T1DM patients who already face many restrictions on a daily basis. Personalized treatment approaches seem to be essential for simultaneously managing and optimizing CeD and T1DM. However, the lower compliance to GFD among T1DM patients suggests the need for further research to provide support for long-term management of both T1DM and CeD.

Keywords: celiac, CeD, T1DM, diabetes, gluten

INTRODUCTION

Celiac disease (CeD) is categorized as an autoimmune condition that develops in genetically predisposed individuals, characterized as a T-cell-mediated enteropathy triggered by gluten exposure [1]. Gluten, a complex of prolamin proteins including gliadins in wheat, hordeins in barley, secalins in rye, and avenins in oats, exhibits unique structural properties due to disulfide and hydrogen bonding along with a high content of proline, which triggers an immune reaction in CeD-susceptible individuals [2]. CeD affects approximately 0.5 to 1% of the world's population. The prevalence is rising, particularly among women and children, due to increased awareness of the condition and improved access to screening [3]. In its typical manifestation, CeD usually begins shortly after introducing gluten to the diet, around the age of 6 months in most cases. It often presents as chronic diarrhea and passage of voluminous

stools, accompanied by additional symptoms such as loss of appetite and lethargy. Among other common signs are recurrent vomiting, poor appetite, constipation, delayed growth or puberty, short stature, and irritability-all of which should suggest the need for immediate screening for CeD. During physical examination, patients may show signs of abdominal bloating, malnutrition and disruptions in the weight growth curve [4]. Nutritional deficiencies related to malabsorption in CeD can lead to numerous clinical signs. Iron deficiency usually causes microcytic, hypochromic anemia, while vitamin B12 and folate deficiencies are associated with megaloblastic anemia. Vitamin D deficiency in CeD patients may be associated with bone deformities, osteomalacia, osteoporosis, cognitive dysfunction, and secondary hyperparathyroidism. Zinc deficiency can cause growth restriction, hypogonadism, infertility, impaired sense of taste, poor wound healing, diarrhoea, dermatitis, glossitis, alopecia and corneal opacity. Also, protein deficiency can lead to oedema and muscle wasting [1].

T1DM is an autoimmune disease in which pancreatic β-cells are destroyed by a T-cell mediated autoimmune response, leading to the complete inability of the pancreas to produce insulin, resulting in chronic hyperglycemia. It affects approximately 30 million people worldwide, accounting for 10% of all diabetes cases and typically presents in childhood or adolescence. Its rising occurrence worldwide causes significant personal challenges due to the necessity of lifelong insulin therapy. Chronic hyperglycemia can result in both microvascular and macrovascular complications, reducing life expectancy and seriously impairing quality of life unless properly managed [5, 6]. One of the most serious complications of T1DM is diabetic ketoacidosis (DKA). It occurs either as an onset of newly diagnosed T1DM or in known cases, mostly precipitated by events like stress, infection, or inappropriate management of insulin therapy. It results from absolute deficiency of insulin, which prevents the entrance of glucose into the cells. The liver then degrades fat into energy, which results in ketone production at large amounts and acidification of the blood [7]. DKA is still a leading cause of death among children. The mortality rates for DKA vary from 0.15% to 0.35% in developed countries like the United States, Canada, and the United Kingdom. In contrast, rates are significantly higher in developing countries like India, Pakistan, and Bangladesh, ranging between 3.4% and 13.4% [8].

Patients with T1DM are at an increased risk of developing other autoimmune diseases, especially autoimmune thyroiditis and CeD which are the most common. Other autoimmune

diseases that can occur include systemic lupus erythematosus, rheumatoid arthritis, autoimmune gastritis and Addison's disease [9]. The occurence of CeD is significant in the T1DM population, reaching 5% of those affected, making it one of the most common autoimmune diseases to co-occur in this population [10].

COMMON PATHWAYS IN THE DEVELOPMENT OF T1DM AND CeD

The association of T1DM and human leukocyte antigens (HLA) is well established, especially with DR4-DQ8 and DR3-DQ2 which are found in a significant number of children diagnosed with T1DM. Similarly, individuals positive for HLA-DQ2 and HLA-DQ8 are frequently diagnosed with CeD [11]. Despite the established connection between specific HLA genes and the development of T1DM in genetically predisposed individuals, most people carrying these genes will never develop T1DM or CeD [10]. There's growing research that indicates there are many other factors, such as various different genetic predispositions, immune system irregularities related to microbiome, environmental influences, viral infections, and dietary factors, that may be significant in the development and co-occurrence of T1DM and CeD [12].

The gut microbiome plays a key role in the immune dysregulation underlying both T1DM and CeD. Research has shown that microbial composition, specifically reduced Firmicutes and Bacteroidetes, with increased Lactobacillus species, via the adaptor molecule MyD88, impacts autoimmune diabetes. Other microbes, like Lactobacillus johnsonii also regulate immunity by augmenting intestinal barrier integrity, otherwise promoting the differentiation of Th17. In CeD, Th17 cells react to gliadin, increasing IL-17A production and mucosal inflammation. Similarly, microbial imbalances in T1DM disrupt immune tolerance, contributing to beta-cell autoimmunity. These shared pathways highlight the microbiome's role in linking T1DM and CeD through immune dysregulation and inflammation [13].

Viral infections are another factor linked to the development of both T1DM and CeD [12]. Research conducted in Germany, based on data analyzed from nearly 300,000 infants, shows that viral infections in the first year of life may increase the risk of developing CeD in the future [14]. Kemppainen et al. came to similar conclusions after investigating data regarding infections in children from the USA and Europe who were genetically predisposed to CeD. Their findings revealed that children who had recurrent respiratory or digestive

system viral infections were at higher risk of developing CeD. The risk was altered by various factors, such as: gluten intake, breastfeeding and rotavirus vaccination record. Children who were vaccinated against rotaviruses had lower risk of developing CeD [15]. Seasonality in T1DM appears to be linked to seasonal respiratory and enteroviral infections during colder months. While viral infections play a significant role, other seasonal environmental factors, such as reduced sun exposure and dietary changes also contribute. These factors seem to have a more pronounced effect in individuals genetically predisposed to T1DM, who are particularly susceptible to developing islet cell autoantibodies during enteroviral infections compared to those without the genetic risk [16].

Gluten plays a significant role in linking T1DM and CeD due to its effects on immune responses, gut permeability, and inflammation. In CeD, gluten triggers an autoimmune reaction through gliadin, a protein found in gluten, leading to intestinal inflammation and tissue damage. Similarly, studies suggest that gluten may influence T1DM development by promoting gut inflammation, increasing intestinal permeability, and contributing to immune dysregulation. This heightened permeability allows gliadin to interact with the immune system, potentially triggering beta-cell autoimmunity in genetically predisposed patients [11]. Research in animal models highlights gluten's role in T1DM development, showing that a gluten-free diet can significantly reduce the incidence of T1DM [17]. Additionally, maternal gluten intake during pregnancy and early-life exposure to gluten have been associated with an increased risk of T1DM in children, further emphasizing its influence on both conditions [18]. These findings indicate that gluten not only contributes to the development of CeD but may also serve as a trigger for T1DM.

CLINICAL MANAGEMENT

In patients with T1DM, classic symptoms of CeD mentioned above are often absent. However, some may experience mild gastrointestinal symptoms which are more significant in comparison to T1DM patients without CeD. Whether CeD presents with symptoms or remains asymptomatic, it can still lead to complications in children with T1DM, such as impaired growth and delayed sexual development, specifically in the pediatric population [13].

Given the significant prevalence of CeD among individuals with T1DM, it is recommended that all patients undergo screening for CeD. The diagnosis of CeD is based on

widely recommended screening protocols and most commonly made through the measurement of IgA anti-tTG combined with the measurement of total serum IgA, which is later confirmed by EMA testing. If IgA deficiency is present, which is more common in CeD patients than in the general population, IgG anti-tTG should be tested [19]. Screening should be performed at the following times: at the time of diabetes diagnosis, annually for the first 4 years of follow-up, and every 2 years for the remaining 6 years of follow-up. If CeD-related antibodies are found, a bowel biopsy, which is a gold standard, must be performed to confirm the diagnosis of CeD [20]. The endoscopic biopsy should be performed in the duodenal bulb and the second portion of the duodenum. It is recommended to take at least four biopsies, with two samples from each of the sites specified [21].

The treatment of CeD in diabetic patients is the same as for all patients with CeD. A strict gluten free diet (GFD) should be introduced in patients with serological and histological proof of CeD. Patients should meet a dietician regarding the GFD education and to address any potential nutritional deficiencies [13]. Some nutritional deficiencies may remain even after long-term adherence to a GFD [22]. Most patients with symptoms will see improvement within 2-4 weeks of starting the GFD diet. Serological tests should be performed after 3-4 months and then annually once they are normalized [13]. Individuals with diabetes and untreated CeD often exhibit a lower body mass index and reduced HbA1c levels compared to those with diabetes alone. The weight loss associated with untreated CeD may contribute to better glycemic control. However, transitioning to a GFD improves nutrient absorption in the intestines, leading to an increased insulin requirement. Studies have shown that adhering to a gluten-free diet can help reduce the frequency of hypoglycemic episodes while maintaining optimal glycosylated hemoglobin levels [11]. Even though the GFD is getting gradually less difficult to introduce because of the easier access to gluten free products, it could pose a challenge for T1DM patients. A lot of gluten free products have a high glycemic index which could have a negative impact on glycaemia management, HbA1c levels and lipid profile, which ultimately could lead to chronic vascular or renal complications. Apart from that, patients with T1DM are usually on a dietary regimen, thus introducing the GFD on top of another diet and trying to mix them could pose a challenge. That’s why the adherence to a GFD is a common challenge for patients managing both T1DM and CeD. Research shows that only about 60% of individuals with T1DM and CeD strictly follow a GFD, compared to approximately 80% of patients with CeD alone, who manage to follow the GFD [13].

In recent years, the management of autoimmune diseases, including T1DM and CeD, has evolved to a more personalized approach, taking in account each patient's habits and overall well-being to optimize treatment outcomes [24]. This shift towards personalized medicine involves creating a treatment based on the unique biological, genetic, and clinical characteristics of the patient. However, the process becomes more problematic when other factors, such as lifestyle, and environmental influences are taken into account. All of them must be carefully incorporated to enhance therapeutic effectiveness [25].

CONCLUSION

CeD and T1DM are autoimmune disorders that tend to co-occur in a significant number of T1DM patients also being diagnosed with CeD. Both CeD and T1DM share a common genetic foundation, particularly the presence of HLA-DQ2 and HLA-DQ8. Despite the common genetic predisposition, exact mechanisms of their co-occurrence are complex and involve other factors related to viral infections, microbiome, immunology and environmental factors. The role of gluten further links T1DM and CeD by triggering the immune response in both diseases, specifically by influencing the development of T1DM through immune dysregulations and increasing the permeability of the gut. Because of the high prevalence of CeD in T1DM patients, early screening is recommended, starting at the time of diagnosis and continuing periodically in the following years. Diagnosis is confirmed through serological tests and duodenal biopsy. The management of CeD in T1DM involves a GFD which often leads to improvement among symptomatic patients within weeks. However, introducing the GFD might be a challenge among T1DM patients, as it can affect glycemic control and increase the insulin requirements due to better processing of the nutrients. Personalized medicine plays a significant role in treating T1DM and CeD patients, as it implements individual treatment plans taking various, complicated factors into consideration. However, it could become difficult to manage when factors such as lifestyle and environmental influences are acknowledged. Patients tend to have a significant problem sticking to the GFD, with lower compliance among T1DM and CeD patients compared to those with CeD by itself, which highlights the importance of further research and strategies to support long-term dietary adherence. Despite these challenges, a personalized approach to treating T1DM and CeD

might optimize treatment outcomes and improve the quality of life for patients trying to manage both T1DM and CeD.

DISCLOSURE

Author Contributions:

Conceptualization, WF, and JŚ; methodology, WF, UZ, JD; software, KD, JŚ; check, GT, WD and MP; formal analysis, JD, WF, SA; investigation, SA, KS; resources, JW, WF, GT, WD; data curation, WF, KS, JW; writing - rough preparation, WF, JD, JŚ; writing - review and editing, WF, UZ, KD, MP; visualization, UZ, GT, WD; supervision, WF, JD; project administration, KD, WD, JW, JŚ, SA, UZ;

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