DOI: https://doi.org/10.53555/nnmhs.v8i12.1460 Publication URL: https://nnpub.org/index.php/MHS/article/view/1460

ASSOCATION DIABETES MELLITUS AND CELIAC DISEASE : ASYSTEMATIC REVIEW

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Abstract

The incidence of diabetes mellitus, a persistent metabolic condition, has been steadily climbing at an alarming rate all over the world. This condition represents a substantial danger to the wellbeing of people living in all parts of the world. Celiac disease is an immune-mediated condition that affects a person for their entire life. It is characterized by gluten-triggered inflammation and morphological damage of the small bowel mucosa in genetically susceptible individuals. Celiac disease can be prevented by avoiding foodsthat contain gluten. One of the surprising revelations that came out of this latest investigation was the realization that type 1 diabetes is significantly overrepresented in particular in males who have celiac disease. On the other hand, the prevalence of type 2 diabetes was practically identical to that of the overall Finnish population. People who have celiac disease and also have type 1 or type 2 diabetes are more likely to experiencesevere comorbidities, and type 1 diabetes is associated with a poorer rate of adherence toa gluten-free diet than celiac disease alone. 16 According to the findings of this study, patients who have type 1 diabetes have an incidence of CeD that is up to twice as high. This is connected to autoimmune disease, which is the pathophysiology of type 1 diabetesas well.

Keyword: *Autoimmune; Celiac disease; Diabetes Mellitus; Hyperglycemia*

INTRODUCTION

Diabetes mellitus is a chronic metabolic ailment that has been rapidly increasing in incidence all over the world. This condition poses a significant threat to the health of communities everywhere.[1] Celiac disease (CD), a chronic autoimmune disease, is characterized by small intestinal inflammation and villous atrophy (VA), both of which are induced by gluten exposure in genetically susceptible individuals.[2] The prevalence ofCeliac disease in western European countries is approximately one in one hundred. According to the findings of a recent meta-analysis, greater than one in twenty patients diagnosed with type 1 diabetes (T1DM) also had celiac disease as proven by biopsy.[3]

Celiac disease is an immune-mediated disorder that lasts a person's entire life and is characterized by gluten-triggered inflammation and morphological damage of the small bowel mucosa in genetically susceptible individuals.[4] Celiac disease is an autoimmune disorder that affects the small intestine. With a prevalence that is currently believed to range anywhere from 1% to 2% among Western populations. In addition to this, it has a disproportionately high prevalence in type 1 diabetesmellitus, which has a common genetic tendency with CeD.[5,6]

Despite the fact that this link is well recognized, particularly in children, the effectof simultaneous T1DM on the clinical and histological presentation in patients with celiac disease in adults is still unknown. In contrast to T1DM, non-autoimmune-mediated type2 diabetes (T2DM) is not regarded to be overrepresented in celiac disease.[7] Celiac diseaseis an autoimmune disorder that causes celiac disease. In point of fact, study recently revealed that the prevalence of T2DM was much lower among individuals with celiac disease than it was in the general population of the United States, indicating a possible protective impact.[8,9]

It stands to reason that their discovery ought to be validated in other countries. Inaddition, very little research has been done to investigate how the presence of simultaneous diabetes affects the symptoms and progression of celiac disease in adult patients.[8,9] This article explores the link between diabetes mellitus and celiac disease andprovides some supporting evidence.

METHODS

The full-text papers written in English were used as the source material for the data that was gathered for the purpose of conducting this systematic review. The review'spurpose was to determine association between diabetes mellitus and celiac disease (CeD). During the process of producing this essay, the databases Pubmed and Google Schoolar were utilized extensively throughout the research phase. The following was mentioned among the conditions for eligibility: (1) A cohort study, cross-sectional study, or case– control study that reported the risk of CD among patients with psoriasis compared with participants who did not have psoriasis; (2) A relative risk, hazard ratio, incidence ratio (IR), or standardized IR with 95% confidence intervals (CIs), or sufficient data to calculate those ratios were provided.

Table 1. The litelature include in this study

Author	Origin	Method	Sample Size	Result
Kylokas, 2016[10]	Finland	Cross sectional	1,358 celiac patients	The prevalence of type 1 diabetes (men/women) was 8.0% /1.8% in celiac patients and 0.7% /0.3% in thecommunity, and that of type 2diabetes 4.3% /2.5% and 4.4% /3.0%, respectively.Celiac patients with concomitant type 1 diabetes were younger (45 years vs 65 years and 52 years, P 0.001), more frequently detected through screening (43% vs 13% and 14%, P <0.001), had fewer other gastrointestinal diseases (8% vs 40% and 25%, P = 0.028), more thyroidal diseases (18% vs 16% and 13%, P = 0.043), and lower dietary adherence (71%vs 95% and Patients with concomitant type 2 diabetes had more hypercholesterolemia thanthe other groups (8 % vs 6 % and 4 %, P = 0.024), and bothdiabetes groups more hypertension (47 % and 31 %vs 15 %, P < 0.001) and coronary artery disease (29 %and 18 % vs 3 %, P < 0.001) than the patients with celiac disease only.
Kirilgul, 2017[11]	USA	Clinical trial	135	Gender, age, body mass index(BMI) and tTGA IgA, kreatinin, calcium, LDL- cholesterol (LDL-C), total cholesterol, 25-OH vitamin D3 levels were similar between groups. Systolic and diastolic blood pressure,waist circumference, fastingplasma glucose, postprandial plasma glucose, urea, sodium,HbA1c, LDL-C, triglyceride,vitamin B12 levels were significantly higher in DM group (p < 0.0001). BMI, high-sensitive CRP, microalbuminuria, and AST, ALT, potassium, phosphorus levels were significantlyhigher in the T2DM group (p< 0.05). HDL-cholesterol and parathormone levels weresignificantly lower in the T2DM group (p < 0.05). Twoof the 135 patients with T2DM were diagnosed with CD (1.45%).
Craig, 2017[12]	Australia	Prospective study	52,721	CD prevalence ranged from 1.9% in the T1DX to 7.7% inthe ADDN and was higher ingirls than boys (4.3% vs. 2.7%, P < 0.001). Childrenwith coexisting CD were younger at diabetes diagnosiscompared with those with type 1 diabetes only (5.4 vs.7.0 years of age, P < 0.001) and fewer were nonwhite (15vs. 18%, P < 0.001). Height SDS was lower in those with CD (0.36 vs. 0.48, adjusted P< 0.001) and fewer were over weight/obese(34vs.37%, adjusted P < 0.001), whereas mean HbA1c values were comparable: 8.3 ± 1.5% (67 ± 17 mmol/mol) versus 8.4 ±1.6% (68 ± 17 mmol/mol).
Gokalp, 2011	Iran	Cross sectional	137consecutive patients with type 1 DM, 172 with type 2 DM and 113 age-sex matched control subjects	AGA IgG positivity was detected in 38.7% (53/137) patients with type 1 DM in 26.2% (45/172) patients with type 2 DM and in 16.8% (19/113) control subjects (significant differences).AGA IgA positivity was detected in 24.8% (34/137) patients with type 1 DM, in 9.3% (16/172) patients with type 2 DM and in 3.5% (4/113) control subjects (significant differences).EMA IgG positivity was detected in 10.2% (14/137) patients with type 1 DM in 0.6% (1/176) patients with type 2 DM and 0.9% (1/113) control subjects (significant differences). EMA IgApositivity was detected in 11.7% (16/137) patients with type 1 DM in 0.6% (1/172) patients with type 2 DM and in none of control subjects.EMA IgA positivity was significantly higher in patientswith type 1 DM as compared with patients with type 2 DM and controls.

The keywords used in the search were “diabetes mellitus” and “celiac disease”. We include study conducted above in 2010-2022. This analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) paradigm, in which the researchers originally entered keywords into each database. The phrases : ((“diabetes mellitus”[MeSH Terms] OR “diabetes mellitus”[All Fields]) AND (“coeliac disease”[All Fields] OR “celiac disease”[MeSH Terms] OR (“celiac”[All Fields] AND “disease”[All Fields]) OR “celiac disease”[All Fields])) AND ((y_5[Filter]) AND (clinicaltrial[Filter] OR randomizedcontrolledtrial[Filter])) used in this study. We received two articles, which will be discussed during the discussion **(Table 1)**.

RESULT

First study in Finland showed prevalence of type 1 diabetes (men/women) was 8.0% /1.8% in celiac patients and 0.7% /0.3% in the community, and that of type 2 diabetes 4.3% /2.5% and 4.4% /3.0%, respectively. Celiac patients with concomitant type 1 diabetes were younger (45 years vs 65 years and 52 years, P <0.001), more frequently detected through screening (43% vs 13% and 14%, P <0.001), had fewer other gastrointestinal diseases (8% vs 40% and 25%, P = 0.028), more thyroidal diseases (18% vs 16% and 13%, P = 0.043), and lower dietary adherence (71% vs 95% and Patients with concomitant type 2 diabetes had more hypercholesterolemia than the other groups (8 % vs 6 % and 4 %, P = 0.024), and both diabetes groups more hypertension (47 % and 31 % vs 15 %, P < 0.001) and coronary artery disease (29 % and 18 % vs 3 %, P < 0.001) thanthe patients with celiac disease only.[10]

Kizigul, *et al* showed systolic and diastolic blood pressure, waist circumference, fasting plasma glucose, postprandial plasma glucose, urea, sodium, HbA1c, LDL-C, triglyceride, vitamin B12 levels were significantly higher in DM group (p < 0.0001). BMI, high-sensitive CRP, microalbuminuria, and AST, ALT, potassium, phosphorus levels were significantly higher in the T2DM group (p < 0.05). HDL-cholesterol and parathormone levels were significantly lower in the T2DM group (p < 0.05). Two of the135 patients with T2DM were diagnosed with CD (1.45%).[11]

Craig study showed CD prevalence ranged from 1.9% in the T1DX to 7.7% in the ADDN and was higher in girls than boys (4.3% vs. 2.7%, P < 0.001). Children with coexisting CD were younger at diabetes diagnosis compared with those with type 1 diabetes only (5.4 vs. 7.0 years of age, P < 0.001) and fewer were nonwhite (15 vs. 18%,P < 0.001). Height SDS was lower in those with CD (0.36 vs. 0.48, adjusted P < 0.001) and fewer were overweight/obese (34 vs. 37%, adjusted P < 0.001), whereas mean HbA1cvalues were comparable: 8.3 ± 1.5% (67 ± 17 mmol/mol) versus 8.4 ± 1.6% (68 ± 17 mmol/mol).[12]

Fourth study showed AGA IgG positivity was detected in 38.7% (53/137) patients with type 1 DM in 26.2% (45/172) patients with type 2 DM and in 16.8% (19/113) control subjects (significant differences). AGA IgA positivity was detected in 24.8% (34/137) patients with type 1 DM, in 9.3% (16/172) patients with type 2 DM and in 3.5% (4/113) control subjects (significant differences). EMA IgG positivity was detected in 10.2% (14/137) patients with type 1 DM in 0.6% (1/176) patients with type 2 DM and 0.9% (1/113) control subjects (significant differences). EMA IgA positivity was detected in 11.7% (16/137) patients with type 1 DM in 0.6% (1/172) patients with type 2 DM and in none of control subjects. EMA IgA positivity was sig- nificantly higher in patients withtype 1 DM as compared with patients with type 2 DM and controls.[13]

DISCUSSION

CD is an uncommon form of autoimmunity for two reasons: first, the primary antigen that triggers the condition can be identified, and second, CD is the only form of autoimmunity that can be reversed by avoiding the food that contains the triggering antigen. Autoimmunity is caused by antigenic pieces of gluten that pass through the small bowel epithelium either directly via a leaky or damaged epithelium or indirectly via othermechanisms such as transcellular transport. This can happen either directly or indirectly. Glutens are exceptionally resistant to the enzymatic breakdown that occurs in the intestines, and as a result, significant amounts of gluten can build up in the lumen.[14]

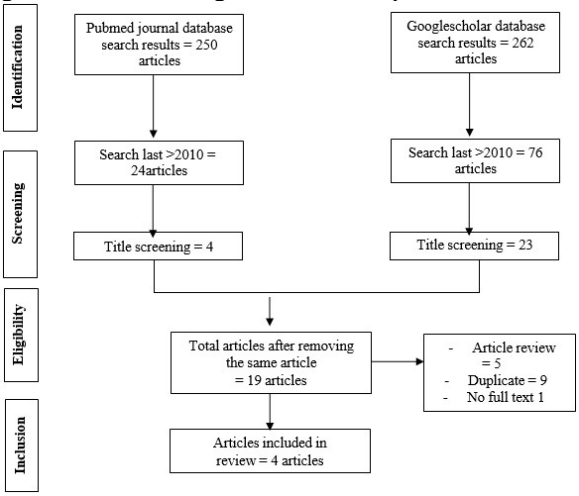

Figure 1. Article search flowchart

The discovery that T1DM is considerably overrepresented specifically in men with celiac disease is one of the novel findings of the current investigation.[1,15] On the other hand, the prevalence of T2 DM was essentially similar to that of the Finnish population in general. In addition, people with celiac disease who simultaneously have type 1 or type 2 diabetes are more likely to experience severe comorbidities, and type 1 diabetes is associated with a poorer rate of adherence to a gluten-free diet.[16,17]

The total prevalence of T1DM was 3.8% among patients with celiac disease who were above the age of 30. Even in Finland, where the incidence of type 1 diabetes is one of the highest in the world, this is a considerable overrepresentation when compared to the population as a whole. In contrast to our research, the vast majority of the earlier investigations into the possible link between celiac disease and T1DM were carried out on children, in whom the characteristics of the two diseases may have been different.[18]

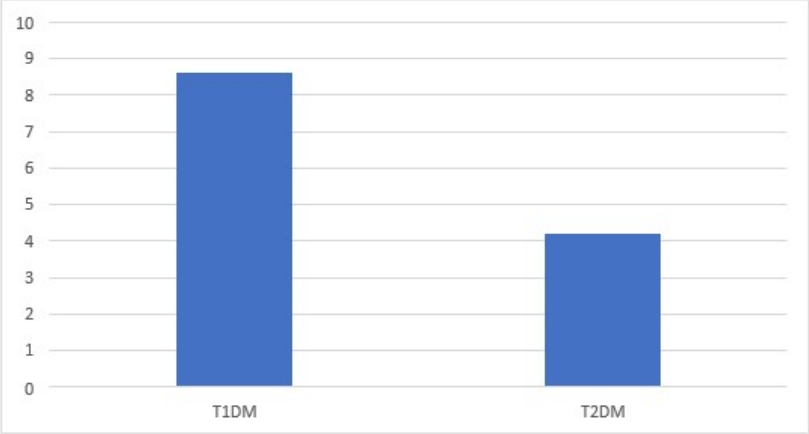

Figure 2. Percentage CeD in DM patients

T1DM It is interesting to note that the male-to-female ratio of T1DM varies between age groups and that it is higher in countries where T1DM is more prevalent. It has also been noticed that this ratio is higher in nations where T1DM is more common.[17]This latter possibility may help to explain, at least in part, the larger proportion of T1DMmen seen in our study sample; nevertheless, additional research is required to fully explain these gender differences. Additionally, the prevalence of T1DM was approximately five times greater in men with celiac disease who were between the ages of 30 and 64 compared with men who were 65 or older.[19]

The higher mortality rate associated with DM1 may be to blame for the decreasedprevalence of DM1 among older celiac patients. Therefore, it has been demonstrated thatpeople with diabetes type 1 who also have celiac disease and have had it for more than 15 years have a higher risk of death when compared to patients who have only diabetes type 1. The higher prevalence of DM1 among younger men in this region might possibly be partially attributable to the rising incidence of DM1 throughout the course of time at the population level.[19,20]

In Finland, celiac patients have, on average, a rather short diagnostic delay and a mild clinical picture, whereas in patients from the United States, the classical malabsorptive disease, which is associated with weight loss, is still common. This discrepancy in the results could be explained by differences in the presentation of the disease.[5] At the time of diagnosis, Finnish patients typically have a normal weight or are even overweight; hence, one could argue that their risk for developing type 2 diabetes is"normal". On the other hand, in the study conducted in the United States, the protective impact of celiac disease was observed even after correcting for malabsorption, symptoms, and BMI; this suggests that there are additional factors that contribute to the disparate findings. The selection of the control group and the overall prevalence of type 2 diabetesin the population are both potential factors that could have an effect.[3]

T1DM and CD have an obvious immune link because they both share an abnormal immune response of the intestinal mucosa, intestinal inflammation with varying degrees of enteropathy, and the production of tTGA.[20] Rectal gluten challenge causes a significantincrease in CD3+ and/ lymphocytes in the rectum mucosa of T1DM patients as well as CD patients, whereas these immunohistochemical changes were not observed in controls. Furthermore, small intestinal biopsies from T1DM and CD patients cultured in vitro with gliadin revealed a significant increase in CD3+ T lymphocytes in the epithelium, as well as CD25+ mononuclear cells and CD80+ cells in the lamina propria, as well as increasedexpression of HLA-DR molecules in the crypts.[16]

These signs of immune activation were not seen in T1DM patients' intestinal biopsies cultured with food proteins other than gliadin, and they were also absent in HLA-DQ2 nondiabetic subjects.[21] Furthermore, regardless of small intestine morphology, patients with T1DM had a higher density of IL-1- and IL-4-positive cells in the lamina propria of the duodenum. Increased tTGA synthesis has been observed in NOD mouse duodenal biopsies, but the underlying mechanism remains unknown. Furthermore, IgA deposits of tTGA have been found in the small intestinal biopsy of the majority of T1DMpatients, which are predictive markers of CD onset.[22]

The expression of gut-associated homing receptor by islet-infiltrating autoreactive cells in NOD mice and patients with T1DM and no CD suggests that lymphocytes may recirculate between the gut and the pancreas. The frequent coexistence of CD and T1DM appears to be more than a coincidence, implying a unifying hypothesis on the development of both disorders, with gluten playing a central role in their pathogenesis.[22] In this regard, eliminating

dietary gluten after a CD diagnosis is linked to a lower frequency of T1DM. Undiagnosed CD may contribute to the onset of T1DM by activatingthe gut immune system and increasing the permeability of the intestinal barrier to largeproteins, as well as enteral viruses, particularly coxsackievirus B. Furthermore, in NODmice that had never been exposed to gluten, a gluten-free diet (GFD) delayed, and to a large extent prevented, diabetes.[22]

CONCLUSION

According to the findings of this study, patients who have type 1 diabetes have anincidence of CeD that is up to twice as high. This is connected to autoimmune disease, which is the pathophysiology of type 1 diabetes as well.

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