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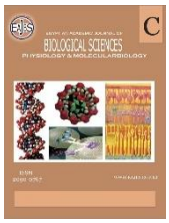

Relation between Variation in Biomarkers of Celiac Disease and Presence of Diabetic Type-1: A Single Center Experience

Hind A. Alzahrani
Basic Sciences, Applied Medical Sciences, Albaha University, Albaha 4781, Saudi Arabia
***E-mail:** hindalzahrani@bu.edu.sa

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ABSTRACT

Background: Type 1 diabetes (T1D) and celiac disease are the most common related autoimmune disorders. There is clinical and pathological overlap between CD and type 1 diabetes T1D, two autoimmune illnesses. Approximately 8% of people with T1D had a mean prevalence of CD. Since T1D patients may not exhibit the classic intestinal symptoms of CD, active case discovery is advised in this higher-risk population. Sensitive and particular serologies, such as tissue transglutaminase (tTG) IgA, deaminated gliadin peptide (DGP) IgA, and IgG, are used for screening. **Aim:** The study aimed to find the relation between celiac disease biomarkers variation in diabetic type 1. **Methods:** This retrospective study included all patients diagnosed with CD from January 2022 to June 2023 at King Fahad Hospital in Al-Baha City, Saudi Arabia.**Results:** The study included 209 participants; of them 56.5% were males, and the average age of the participants was 13.2±6.1 years. Nearly half of the particpants (52.2%) were diagnosed as they have Diabetic type 1. Most of the participants were seronegative for biomarkers of celiac disease. No statistically significant difference between demographic data and seropositivity for celiac diseases. There was a higher proportion of seropositivity among non-diabetic participants compared to those diagnosed with T1D with no significant difference. **Conclusion and recommendation:** The prevalence of seropositivity for CD markers was low among patients diagnosed with T1D, however, healthcare professionals must be mindful of screening these patients to prevent the potential risks associated with CD, such as microvascular complications and other related health issues.

INTRODUCTION

Celiac disease (CD) and type 1 diabetes mellitus (T1D) are classified as autoimmune disorders which are mostly determined by HLA genetics and are commonly associated with one another. Given the increased global prevalence of these conditions, studies indicate that other factors such as environmental factors, the gut microbiota, and other infectious agents, may contribute to the development of those genetic disorders (Aktay *et al.,* 2001). The CD is a polygenic autoimmune-mediated enteropathy that is triggered by the consumption of gluten in the diet and is characterized by a marked increase in a specific serum antibody level, while on the other hand, T1D is characterized by the destruction of beta cells in the pancreas due to an inappropriate autoimmune response, leading to the failure of maintaining normal physiological blood glucose levels. It is currently advised to screen for CD in T1D patients and vice versa to improve understanding and care for both conditions (Camarca *et al.,* 2012).

The CD is an autoimmune inherited disease that results in inflammatory damage to intestinal epithelium upon the consumption of gluten (*Scaramuzza et al., 2013*). Since only 30–40% of individuals exhibit the disease's characteristic appearance, it is recommended to use a combination of antibody levels and biopsy samples to confirm the diagnosis. For a typical population, the incidence rate in most nations ranges from 1:120 to 1:300 (Amin *et al.*, 2002).

Since the initial reports of celiac disease in 1969, numerous studies have established an association between CD and T1D, indicating that people with diabetes have a 5-7 times higher risk of developing CD than the general population *(Guvenc et al., 2002*). According to recent studies, 1 to 8% of individuals with T1D also have CD. Furthermore, other studies show that T1D have a 20-fold increased risk of developing CD (Farrell, 2012). Saudi Arabia is now ranked eighth in the world due to the high T1D prevalence rates. This country is home to an estimated 35,000 children and adolescents who are diagnosed with this disease. In addition, Saudi Arabia has 33 new T1D cases per 100,000 people annually, which ranks it fourth worldwide for the prevalence of new cases. The prevalence of CD in Saudi Arabia is 2.7% by serology and 1.4% by histological biopsy; this is significantly lower than that of T1D. Children with T1D have a 5.5% to 20% prevalence of CD in other Arab countries, whereas the global prevalence ranges from 3% to 12% (El-Metwally *et al.*, 2020).

Due to the rising prevalence of CD in T1D patients despite the absence of symptoms, screening for CD is now advised for all T1D patients once a year for the first four years and once every two years for the following six years. Numerous investigations have been conducted to determine the effectiveness of CD screening in individuals with type 1 diabetes (Catassi *et al.*, 2021). These studies suggested the use of sensitive and specific serological tests, including tissue transglutaminase IgA, endomysial IgA, and deaminated gliadin peptide IgA and IgG antibodies. Approximately 5-10% of patients with T1D tested positive for these antibodies (Craig *et al.*,2017).

The treatment protocol is the same, whether the patient has been solely diagnosed with CD, or in complication with T1D. It is important to implement a strict gluten-free diet (GFD) for individuals who have both serological and histological evidence of CD. However, adhering to the GFD can be challenging for patients with both T1D and CD, and the adherence level of those patients ranges from 25% to 78% *(Ciacci et al., 2019).*

The course of T1D may be affected by treating CD. Diabetes-associated retinopathy and nephropathy are more common in T1D patients with undiagnosed CD, albeit not all research consistently identified this link. Some studies have shown that T1D patients with untreated CD have lower HbA1c and body mass index compared to those without CD (Cohn *et al*., 2014). Regular checkup and adjustment of blood glucose levels is recommended for T1D patients following a GFD as strict compliance to a GFD in CD may enhance the absorption of nutrients and thus raise the insulin required dose. Conversely, inadequately controlled CD increases the risk of hypoglycemia in diabetic patients and hinders the absorption of nutrients, which will lead to weight loss. Generally, it appears that a GFD could be beneficial for patients with T1D and CD. However, further research and understanding in this area is recommended (Catassi *et al.*, 2021).

We expect a high prevalence of seropositive CD among T1D Therefore, this study aims to assess the study aimed to find the relation between CD biomarkers variation in T1D in the Al-Baha region of Saudi Arabia.

MATERIALS AND METHODS

Study Type:

Retrospective study.

Study Population, Sampling, and Setting:

The study using convenience sampling included all patients diagnosed with

CD who attended King Fahad Hospital in Al-Baha City during the period from January 2022 to January 2023 of both genders. The study excluded pregnant women and those diagnosed with type-2 diabetes.

Tool: The data extracted were demographic data, presence of T1D, and Serology biomarkers such as ANTI GILIADIN IgA, ANTI GILIADIN IgG, ANTI TRANSGLUTAMINASE IgA, ANTI ENDOMYSIA IgA. The patients were considered seropositive when all markers were positive.

Statistical Analysis:

The Statistical Package of Social Sciences (SPSS) (version 28) was used to analyze the results. Qualitative data are described as the number and percent. Numerical variables were presented as mean and standard deviation (SD). To compare the two groups of numerical data, the Mann-Whitney test was used, Relation between qualitative data was done using the Chi-square test. A p-value < 0.05 was considered significant.

RESULTS

The study included 209 participants; the average age of the participants was 13.2±6.1 years. More than half of the participants (56.5%) were male, and 52.2% were diagnosed as they have T1D. Most of the participants were seronegative for biomarkers of CD (Table 1).

No statistically significant difference between age, gender, and seropositivity for CD (p-value=.199, and .120 respectively). There was a higher proportion of seropositivity among non-diabetic participants compared to those diagnosed with T1D (11% versus 4.6%) with no statistically significant difference (p-value=.082) (Table 2 & Fig. 1).

Table 1: Demographic data, presence of diabetes, and variation in biomarkers of celiac disease.

Parameters	Total (n=209)
Age (years)	13.2±6.1
Gender	
Male	118 (56.5%)
Female	91 (43.5%)
Diabetes	
Not-diabetic	100 (47.8%)
Diabetic type 1	109 (52.2%)
Biomarkers variation	
ANTI GILIADIN IgA	
Negative	193 (92.3%)
Positive	16 (7.7%)
ANTI GILIADIN IgG	
Negative	193 (92.3%)
Positive	16 (7.7%)
ANTI TRANSGLUTAMINASE IgA	
Negative	193 (92.3%)
Positive	16 (7.7%)
ANTI ENDOMYSIA IgA	
Negative	193 (92.3%)
Positive	16 (7.7%)

Table 2: Relation demographic data, diabetes, and seropositivity markers of celiac disease.

Parameters	Number	Seronegative (n=193)	Seropositive (n=16)	p-value
Age (years)	209	13.1±6.1	15 ±5.5	.199
Gender				
Male	118	106 (89.8%)	12 (10.2%)	.120
Female	91	87 (95.6%)	4 (4.4%)	
Diabetes				
Not-diabetic	100	89 (89%)	11 (11%)	.082
Diabetic type-1	109	104 (95.4%)	5 (4.6%)	

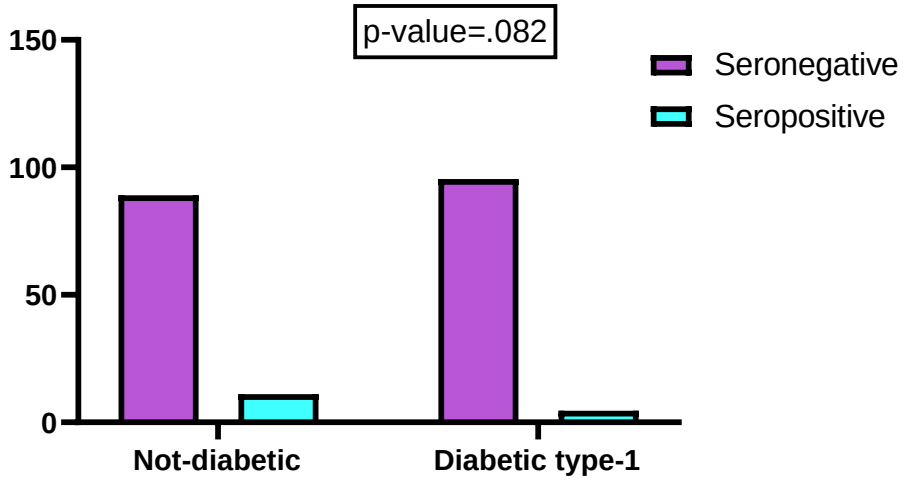

Fig. 1: Relation between markers seropositivity and presence of diabetes.

DISCUSSION

One of the most common autoimmune diseases associated with T1D is CD. The symptoms of this disease include gastrointestinal symptoms, anemia, and growth alterations. CD prevalence in T1D ranges from 3 to 16%, with an average prevalence of 8%. It is worth noting that nearly half of T1D patients may not show any noticeable symptoms of CD (Kang, 2013). Therefore, it is recommended to perform serological screening for CD in all T1D patients to enable early detection of this complication. T1D and CD share similar genetic backgrounds as both conditions involve abnormal immune responses in the small intestine, leading to inflammation and varying degrees of enteropathy (Hill & Holmes, 2008).

The study aimed to find the relation between CD biomarker variations in T1D. The results indicated that there was no significant correlation between gender and the presence of serology biomarkers in T1D, ($P \geq 0.05$). This finding is consistent with a previous study, which suggested that many patients in the early stages of the disease are asymptomatic (Kang *et al.*, 2005). Age was also identified among the factors influencing the correlation between CD and T1D, as recent data from the T1D Exchange Clinic Registry research has recognized and confirmed that autoimmune comorbidities tend to increase with age (Craig *et al.*, 2017). A previous study reported higher rates of CD in adults compared to children, with a 1.5-fold increase in CD rates among adults (Safi, 2018). Therefore, this study found no significant results between T1D and the presence of CD biomarkers when compared to non-diabetic patients. One potential explanation for this lack of correlation could

be the absence of CD screening in adults in the present study.

Nevertheless, other research revealed that CD is substantially more common among first-degree relatives of T1D patients than in the general population, with a prevalence ranging from 4.8 to 6%, (Leeds *et al.*, 2011). As a result, it is advised to conduct serological screening for T1D in first-degree relatives as well. It's still debatable whether other serological screening is necessary for follow-up with tTGA-negative first-degree relatives of T1D (Leffler& Schuppan, 2010).

A previous study investigated the potential role of gender in the presence of CD biomarkers. The findings indicated that there was no significant correlation between gender and CD within both the diabetic and non-diabetic patient groups (Rubio-Tapia, 2013). However, one notable study investigating CD prevalence in individuals with T1D analyzed data from 52,721 young individuals across three continents: Europe (specifically, the United Kingdom, Germany, and Austria), Australia, and the United States (Hughes *et al.,* 2016). Individuals with both T1D and CD were diagnosed with CD at a younger age compared to those with only T1D (5.4 years and 7 years, respectively). Among these individuals, 1,835 individuals, representing 3.5% of the total, had biopsy-proven CD (Shahbazkhani *et al.,* 2004). The median age of CD diagnosis is 8.1 years (ranging from 5.3 to 11.2 years). In 35% of cases, CD was diagnosed within one year after the initial diagnosis of T1D. In 18% of cases, CD was diagnosed roughly within one and two years after the T1D diagnosis (Szaflarska-Popławska, 2014). Three to five years following the diagnosis of T1D, 23% of CD cases were diagnosed. Lastly, 17% of the CD cases were diagnosed more than five years after the initial T1D diagnosis. The incidence of CD exhibited regional variation, ranging from 1.9% in the US to 7.7% in Australia. More importantly, this study noted that the prevalence of CD was significantly higher in females compared to males (4.3% and 2.7% respectively) ($p < 0.001$) (Volta *et al.*, 2010).

In general, numerous studies have indicated a high prevalence of asymptomatic CD among individuals with T1D. Therefore, healthcare professionals must be mindful of screening these patients. This proactive approach is necessary to prevent the potential risks associated with T1D, such as microvascular complications and other related health issues (Walker *et al.,* 2019).

Conclusion and Recommendation: The prevalence of seropositivity for celiac disease markers was low among patients diagnosed with T1D, however, healthcare professionals must be mindful of screening these patients to prevent the potential risks associated with CD, such as microvascular complications and other related health issues.

Limitations of the Study:

A small sample size of the study limits the generalizability of the research and can't prove the high prevalence of seropositive CD among T1D. The study requires a larger number of cases including a more diverse population, such as pregnant women and individuals diagnosed with type 2 diabetes, to improve the generalizability of the findings. Additionally, conducting the study over a longer period may provide more solid and comprehensive results.

Abbreviations:

T1D: Type 1 diabetes
CD: Celiac disease
GFD: strict gluten-free diet
tTG: tissue transglutaminase
DGP: deaminated gliadin peptide

Declarations:

Ethical Consideration: Ethical approval for this study was obtained from King Fahd Hospital in Al-Baha City, approval number (KFH/IRB1109203/7) before the start of the study.

Funding: No funding was received.

Availability of Data and Materials: All datasets analyzed and described during the present study are available from the corresponding author upon reasonable request.

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ARABIC SUMMARY

العلاقة بين التباين في المؤشرات الحيوية المناعية لمرض الاضطرابات الهضمية و مرض السكري من النوع الأول: تجربة مركز واحد

هند الزهراني
العلوم الأساسية، العلوم الطبية التطبيقية، جامعة الباحة، الباحة 4781، المملكة العربية السعوديه

المقدمه: يعد مرض السكري من النوع الأول ومرض الاضطرابات الهضمية من أكثر الامراض شيوعا ضمن الاضطرابات المناعة الذاتية، حيث أن معدل متوسط انتشار الاضطرابات الهضمية لدى المصابين بداء السكري 8٪. ونظرًا لأن مرضى السكري من النوع الأول قد لا تظهر عليهم أعراض المرض، لذلك يُنصح بعمل الاختبارات المناعية بشكل منتظم لمرضى السكري النوع الأول لاكتشاف الحالات النشطة مبكرا.

الهدف: هدفت الدراسة إلى إيجاد العلاقة بين ظهور النتائج الإيجابية لتحاليل المناعية لمرض الاضطرابات الهضمية ومرضى السكري من النوع الأول.

الطرق: شملت هذه الدراسة جميع المرضى الذين تم تشخيص إصابتهم بمرض الاضطرابات الهضمية في الفترة من يناير 2022 إلى يونيو 2023 في مستشفى الملك فهد في مدينة الباحة، المملكة العربية السعودية. ومن ثم تم معرفه المصابين وغير المصابين منهم بمرض السكري النوع الاول وكذالك تسجيل الحالات التي تظهر نتائج إيجابية للاختبارات المناعية و المؤشرات الحيوية للاضطرابات الهضمية.

النتائج: شملت الدراسة 209 مشارك؛ وكان متوسط عمر المشاركين 13.2 ± 6.1 سنة. كان أكثر من نصف المشاركين (56.5%) من الذكور، وتم تشخيص إصابة 52.5% منهم بمرض السكري من النوع الأول. وكان معظم المشاركين سلبيين بالنسبة للمؤشرات الحيوية لمرض الاضطرابات الهضمية. لا يوجد فرق ذو دلالة إحصائية بين البيانات الديموغرافية والإيجابية في التحاليل المصلية للمرضى الماصبين بالاضطرابات الهضمية. بينما كانت نسبة المصابين بالاضطرابات الهضمية والمؤكد إيجابيهم للاختبارات المناعية اعلى عند الغير مصابين بالسكري مقارنة بأولئك الذين تم تشخيص إصابتهم بالسكري من النوع الأول مع عدم وجود فروق ذات دلالة إحصائية.

الاستنتاج والتوصيات: كان معدل الحصول على النتائج الإيجابية للاختبارات المناعية والمصلية لمرض الاضطرابات الهضمية منخفضًا بين مرضى السكري من النوع الأول، عليه يُنصح الطبيب المعالج أن يُجري الفحص الدوري لهؤلاء المرضى لمنع المخاطر المحتملة المرتبطة بمرض الاضطرابات الهضمية، مثل مضاعفات الأوعية الدموية الدقيقة وغيرها من المشاكل الصحية ذات الصلة وذالك لإشارة العديد من الدراسات السابقة بأصابة مرضى سكري من النوع الأول بالاضطرابات الهضيمية بدون ظهور اعراض في المراحل الأولى من تاريخ المرض.