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Celiac Disease in Patients with Type 1 Diabetes Mellitus: Genetics, Biochemical Features, and Serological Markers

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Annotation: The prevalence of celiac disease (CD) is significantly higher in patients with Type 1 diabetes mellitus (T1DM) compared to the general population and as a result, the interrelationship of these two autoimmune disorders has attracted the interest of many researchers over the years. The most pressing questions have been whether the concomitant existence of CD pose challenges to the management of T1DM. Therefore, this study evaluated the diagnostic parameters for T1DM in patients with T1DM and CD. Forty-five patients with T1DM only, 45 with T1DM + CD were recruited for this study and their demographical, anthropometric, biochemical features, and expression of HLA-DQ2 and DQ8 genes were measured. Serum levels of anti-glutamic acid decarboxylase (GAD) autoantibody and c-peptide were also evaluated. The results obtained showed significant differences in ferritin (6.31±0.83 µg/L T1DM vs. 5.43±0.31 µg/L T1DM + CD), vitamin D3 (7.15±0.99 ng/mL T1DM vs. 11.04±2.82 ng/dL T1DM + CD), urea

(35.23±4.36 mg/dL T1DM vs. 23.24±4.75 mg/dL T1DM + CD) and creatinine (1.06±0.06 mg/dL T1DM vs. 0.61±0.01 mg/dL T1DM + CD). Homozygosity to HLA-DQ2 was 11% in T1DM against 31.1% in the T1DM + CD group, 80 % of T1DM + CD patients were HLA-DQ2/DQ8 heterozygotes, while 20 % had HLA-DQ2 gene only with none having the HLA-DQ8 haplotype. Homozygosity to HLA-DQ8 was 57.8 % in the T1DM patients. Seropositivity to anti-GAD was 26.6 % in T1DM patients compared to 31.1% in T1DM + CD group. while the proportion of patients with below normal C-peptide levels in the T1DM + CD group was 66.6 % which is lower than 77.7% recorded for the T1DM group. Anti-GAD levels were significantly higher in patients with T1DM only compared with those with CD+T1DM ($p < 0.05$). From the findings, it was inferred that the concomitant existence of T1DM and CD may result to difficulty in glycemic control and the pre-existence of CD may trigger the pathogenesis/ initiation of T1DM. Therefore, this study recommends that the early diagnosis of T1DM should be sufficient to warrant suspicion of subclinical CD.

Keywords: Celiac disease; Type 1 diabetes mellitus; HLA-DQ2; HLA-DQ8; anti-GAD; C-peptide.

Introduction

Type 1 diabetes mellitus (T1DM) and celiac disease (CD) are both autoimmune diseases having similar genetic aetiology as they are associated with the major histocompatibility complex (MHC) class II DQ2 antigen which confers susceptibility to CD and T1DM as well [1, 2]. There are increasing evidences from epidemiological studies revealing cases of concomitant existence of CD and T1DM in pediatric, adolescent and adult population. These studies reported prevalence of CD among T1DM patients ranging from 1.4% in the United kingdom [3], 1.8% in Sweden [4], 2.6% in Italy [5] to as high as 5.1% in Australia [6], 5.9% in Mexico [7] and 6.4% in the United States [8].

With concerns on the spread of cases of comorbidity of these two autoimmune conditions increasing, the Canadian Diabetes Association guidelines recommend targeted CD screening in patients with T1DM who have classic symptoms, such as abdominal pain, bloating, diarrhea, unexplained weight loss or labile metabolic control [9]. However, despite this increased prevalence of CD in patients with T1DM, the absence of symptoms remains the major challenge in establishing the diagnosis of CD in patients with T1DM and as a result, the co-existence of the two diseases goes undiagnosed until clinical manifestations become obvious. Studies have

shown that a higher proportion of patients with diabetes report subtle or no complaints at CD diagnosis [10, 11].

However, the most worrisome concerns are on the implication of the comorbidity of CD and T1DM on the pathophysiological of the individual conditions as well as disease severity and response to treatment. Recent data have emerged and showed that beyond the short-term metabolic and lifestyle implications, a concomitant diagnosis of CD and T1DM may increase the risk for diabetes-related complications [12]. Additionally, evidence suggests that adult patients with both conditions are at higher risk for diabetes microvascular comorbidities, increased mortality and impaired bone health if the CD remains untreated [11].

Interestingly, the pressing questions however, remains whether the screening of CD in T1DM patients is necessary and which of the two conditions is more detrimental or beneficial to the progress and response to treatment of the other. Also, whether the interrelationship between CD and T1DM occurs at the onset of the disorders or results from progression of the disease remains unresolved.

To address this questions the present study identified patients with T1DM alone as well as those with both conditions (T1DM + CD) and assessed their biodemographical characteristics along with distribution of the genetic genes - HLA-DQ 2 and DQ8 haplotype and explored the possible effect of CD on T1DM by analysing the distribution of seropositivity and titers of serum anti-glutamic acid decarboxylase (GAD) and c-peptide in T1DM patients compared to those with CD and T1DM.

Methods

This study is a cross-sectional case-control study on patients with T1DM as well as those having T1DM with CD, recruited from the Diabetes Center in the Al-Hussein Hospital in Karbala between December 2020 and February 2021. A total of 90 patients were recruited and categorised into group A (T1DM only) and group B (T1DM + CD) with the groups having 45 patients each. T1DM and CD were diagnosed based on the criteria set by American Diabetes Association and American College of Gastroenterology Disease [13, 14]. The exclusion criteria included with type 2 diabetes as well as other autoimmune disease such as autoimmune thyroid disease, autoimmune hepatitis, multiple sclerosis e.t.c.

Demographic data were collected through a questionnaire-based interview and blood samples were for whole blood analysis and serum preparation. Biochemical parameters such as glucose, glycated haemoglobin (HbA1c), packed cell volume (PCV), haemoglobin, white blood cells (WBC), platelets, ferritin, calcium, vitamin D3, urea and creatinine were analysed.

Serological quantitative and qualitative determination of the presence of circulating autoantibodies to GAD antigen was carried out by the indirect enzyme linked immune reaction using the Anti-GAD Ab ELISA Kit (DEIA2289, Creative Diagnostics, United States) was used as per manufacturer's procedures. Also, the concentration of c-peptide in the serum samples was determined using Cobas e411 (Roche Diagnostics International AG, Rotkreuz, Switzerland), which is an automatic immunoassay system that utilizes the electrochemiluminescence (ECL) technology.

The CeliacStrip kit (Operon Immuno & Molecular diagnostics, Spain) was utilized for the detection of the presence or absence of haplotypes that encode the HLA-DQ2 and HLA-DQ8, which are the main HLA-haplotypes associated with CD and T1DM. These include DQA1*05 – DQB1*02 – DRB1*03 (HLA-DQ2 [cis] haplotype 1), DQA1*05 – DQB1*0301 – DRB1*11/DRB1*12 (HLA-DQ2 [trans] haplotype 2), DQA1*03 – DQA1*0302 – DRB1*04 (HLA-DQ8). The CeliacStrip test was carried out in three procedures namely; DNA extraction, PCR amplification, as well as Hybridization and development, based on manufacturer's guidelines.

Data analysis was conducted using SPSS (version 24.0). All quantitative variables or numbers were expressed in form of mean +/- standard deviation. Independent student's t- test was used to establish statistical significance in biochemical parameters and antibody titer values between the T1DM patients and those with T1DM + CD.

Results

Out of the 45 T1DM patients recruited, 22 were males and 23 were females. The patients had mean age of 20.49±5.37 years and mean body mass index (BMI) of 26.70±0.84 Kg/m^2. The T1DM + CD group comprised of 45 patients of which 21 were males and 24 were females. The patients had mean age of 21.80±5.47 years and mean BMI of the group was 26.34±0.83 Kg/m^2.

The results obtained from biochemical analysis serum samples from the patients showed that the T1DM group had mean glucose level of 173.74±1.97 mg/dL, which was slightly lower than that of the T1DM + CD group with mean serum glucose level of 174.92±2.76 mg/dL. Mean levels of HbA1c in the T1DM patients with CD only was 7.90±0.24 %, which was slightly higher than that of the T1DM + CD group with mean serum HbA1c of 7.81±0.40 %.

Amongst the other parameters analysed included, mean platelets count, which was 213.44±40.42 x10^3/L in the T1DM group was slightly higher compared to the 207.24±36.79 x10^3/L obtained in T1DM + CD group at $p < 0.05$. Similarly, mean values for ferritin (6.31±0.83 µg/L; T1DM), urea (35.23±4.36 mg/dL; T1DM) and creatinine (1.06±0.06 mg/dL; T1DM) were significantly higher in the T1DM group compared to those obtained in the T1DM + CD group i.e. ferritin (5.43±0.31 µg/L; T1DM +CD), urea (23.24±4.75 mg/dL; T1DM + CD) and creatinine (0.61±0.01 mg/dL; T1DM + CD) ($p < 0.05$). Statistical significant difference was also observed between the T1DM group and T1DM + CD group for serum concentration of Vitamin D3 i.e. (7.15±0.99 ng/L; T1DM) vs. (11.04±2.82 ng/L; T1DM +CD), at $p < 0.05$. The demography and biochemical characteristics of the patients are summerized in Table 1.

Table 1: Demography and biochemical characteristics of the patients.

	T1DM *(mean±SD)*	**T1DM + CD** *(mean±SD)*	**p-value**
Number of participants *(n (%))*	45 (100)	45 (100)	
Gender *(n (%))*			
Male	22 (48.9)	21 (45.1)	
Female	23 (51.1)	24 (53.3)	
Age *(years)*	20.49±5.37	21.80±5.47	0.55
BMI *(Kg/m^2)*	26.70±0.84	26.34±0.83	0.21
Glucose *(mmol/dL)*	173.74±1.97	174.92±2.76	0.64
HbA1c *(%)*	7.90±0.24	7.81±0.40	0.68
PCV	32.98±5.49	32.89±6.01	0.52
Haemoglobin *(%)*	10.48±1.81	10.26±1.76	0.76
WBC *(x 10^9/L)*	6.91±0.61	6.69±0.55	0.61
Platelets *(x 10^9/L)*	213.44±40.42	207.24±36.79	0.08
Ferritin *(µg/L)*	6.31±0.83	5.43±0. 31	0.023*
Calcium *(mg/dL)*	7.66±0.09	7.55±0.93	0.50
Vitamin D3 *(ng/mL)*	7.15±0.99	11.04±2.82	0.01*
Urea *(mg/dL)*	35.23±4.36	23.24±4.75	0.001*
Creatinine *(mg/dL)*	1.06±0.06	0.61±0.01	0.001*

In the T1DM group, 57.8 % of the patients had HLA-DQ8 haplotype while 11.1 % had the HLA-

DQ2 gene, with 31.1 % of the patients having both the HLA-DQ2 and DQ8 haplotypes. The majority of patients with comorbidity of T1DM and CD i.e. 80 %, had both HLA-DQ2 and DQ8 haplotypes, while 20 % had HLA-DQ2 gene only with no patient having the HLA-DQ8 haplotype. The graphical presentation of the HLA haplotypes distribution is presented in Figure 1.

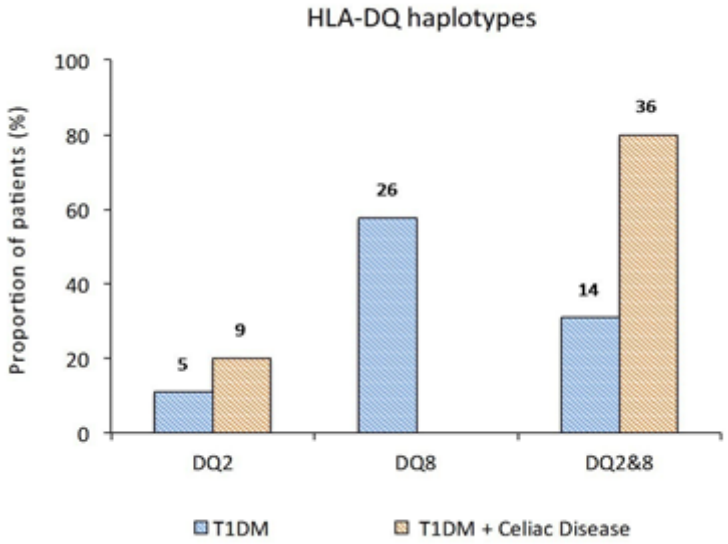

Figure 1: Distribution of T1DM and CD associated HLA haplotypes (HLA-DQ2 & HLA-DQ8) among the study patients.

The proportion of patients having the different HLA haplotypes (DQ2 and DQ8) among the study patients based on their groups. The number of patients under each category is indicated on the respective frequency bar.

The proportion of the patients from both groups that showed positivity to anti-GAD antibodies as well as that of those with C-peptide levels below normal range is presented in Figure 2.

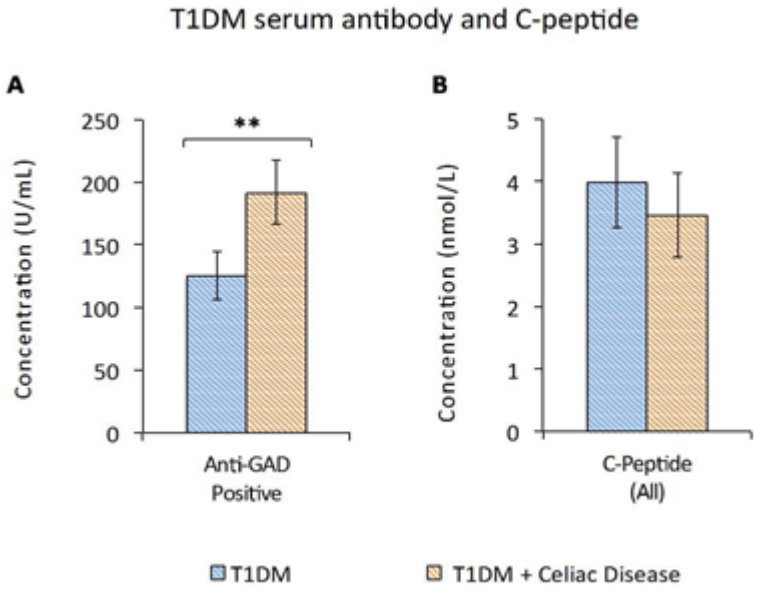

Figure 2: Proportion of patients with positivity to anti-GAD antibody and those with C-peptide levels below normal range.

The frequency of patients from the T1DM as well as the T1DM + CD group which showed

positivity to anti-GAD antibody and C-peptide levels below normal range. The number of patients under each category is indicated on the respective frequency bar.

For the T1DM group, 26.6 % showed positivity to anti-GAD antibody and while 77.7 % had C-peptide levels below the normal range. In the T1DM + CD group, a higher proportion of the patients, i.e. 31.1 % showed positivity to anti-GAD antibody. However, the proportion of patients with below normal C-peptide levels in the T1DM + CD group was 66.6 % which is lower than that recorded for the T1DM group.

For concentrations of T1DM associated antibodies in the serum of patients, mean serum level of anti-GAD antibody in the T1DM group was 125.38±18.92 U/mL which was significantly lower ($p > 0.05$) than the 191.74±25.42 U/mL recorded for the T1DM + CD group. However, for C-peptide, although the mean serum concentration obtained in the T1DM group was slightly higher than that of the T1DM + CD group (i.e. 3.98±0.72 nmol/L [T1DM group] vs. 3.45±0.67 nmol/L [T1Dm + CD]), the difference was not statistically significant at $p < 0.05$. The graphical presentation of the concentration of serum anti-GAD antibody and C-peptide is presented in Figure 3.

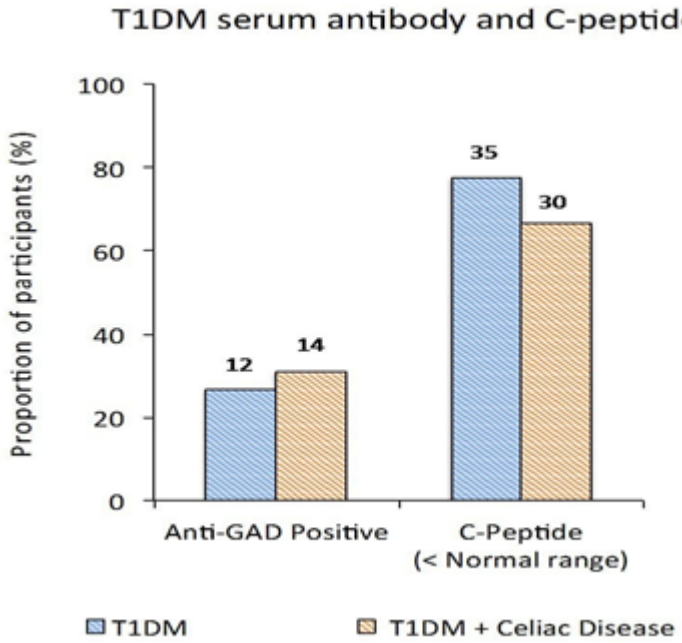

Figure 3: Serum concentrations of T1DM associated antibody (anti-GAD) and c-peptide levels.

The concentration of anti-GAD antibody **(A)** as well as c-peptide **(B)** in serum of patients with T1DM only in comparison with those of T1DM + CD patients. Comorbidity of T1DM with CD increased serum levels of anti-GAD antibody but reduces c-peptide levels.

** indicates statistical significant difference between the groups at $p < 0.05$.

Discussion

The present study investigated the clinical features of T1DM patients and compared these features with those of patients having comorbidity of T1DM and CD. It is however intriguing that despite the randomized, controlled nature of our study population sampling, all the patients in the study were aged on average, between 20 – 21 years and there were no noteworthy differences in their demographical and anthropometric disposition. However, notable differences were observed between the groups with respect to some biochemical parameters. Specifically, glucose levels were not only expectedly higher in T1DM patients but were also observed to be slightly higher in patients having comorbidity with CD. Although there is scarcity of research on biochemical features in CD and T1DM comorbidity, few studies have reported increased blood

glucose levels in T1DM patients with CD [15]. Interestingly however, HbA1c which is an index for measurement of glycemic control was slightly lower in patients with T1DM + CD comorbidity. Studies conducted by Bakker et al, and Aljulifi et al also reported reduced HbA1c in T1DM patients diagnosed with CD compared with those having only T1DM [9, 16]. These differences like in the case of this study, were not statistically significant, thus the observed reduction in HbA1c cannot be an indication of improvement in glycemic control. Patients with T1DM + CD were observed to have anaemic tendencies evident from significantly lower levels of ferritin and low platelet count. Several studies have associated iron deficiency with risk of developing thrombocytopenia in CD patients [17, 18]. Although thrombocytopenia is seldom linked with T1DM, Kumar et al reported a case of thrombocytopenia in an infant at onset of T1DM [19]. Other noteworthy differences observed between the groups were with respect to vitamin D3, urea and creatinine. Both CD and T1DM have been associated with vitamin D deficiencies [20, 21]. This is because vitamin D plays peculiar roles in the onset of CD as well as the pathogenesis of T1DM. Studies have identified vitamin D as a key modulator of immune mechanism and inflammation in the intestinal mucosa barrier [22, 23]. Also, vitamin D is known to suppress T-cell activation through binding with the vitamin D receptor (VDR). Polymorphisms in the VDR gene has been associated with CD [24, 25]. Moreover, early in life supplementation with vitamin D protects against T1DM as vitamin D has been shown to modify T-cell differentiation, regulation action of dendritic cells and induce cytokine secretion, thereby shifting differentiation the balance to regulatory T cells [21]. The serum levels of vitamin D3 recorded was generally low i.e. < 20 ng/mL, however, it was significantly lower in T1DM patients relative to those with CD, suggesting that vitamin D deficiency may be more prominent in T1DM than in CD. Also, it was observed that serum urea and creatinine levels with were otherwise high in T1DM patients was significantly lower in patients with T1DM and CD. Being useful biomarkers for assessing nephropathy in diabetic patients, elevations in urea and creatinine have been correlated with poor glycemic control and indication of end stage renal disease [26]. Interestingly, their reduction in patients with comorbidities as observed in this study could result from molecular-level interplay between the mediators two autoimmune disorders and as such, this is an area requiring further exploration.

The converging point in genetic aetiology of T1DM and CD, as with many other autoimmune disorders, is the human leukocyte antigen (HLA) class II DQ2 gene as its role in genetic susceptibility to T1DM and CD cannot be overemphasized. In this study, the prevalence of HLA-DQ2 and HLA-DQ8 expression among the study groups was analysed. The expression of homozygous HLA-DQ2 was slightly higher among patients with T1DM + CD while expression of homozygous HLA-DQ8 was entirely skewed towards T1DM patients. Also, as expected, expression of heterozygous HLA-DQ2/ DQ8 was largely skewed towards patients having comorbidity of T1DM and CD. The HLA-DQ2 homozygosity has been shown to be associated with 25 - 30 % predisposition to CD among infants [27], while homozygous HLA-DQ8 has been implicated in $CD4^+$ T cell infiltration of islets cells in response against proinsulin thereby increasing susceptibility to autoimmune progression of T1DM [28]. Pociot and McDermott reported 30 % prevalence of HLA-DQ2/DQ8 among patients with T1DM [29], a finding consistent with the result obtained from this study, as 14 out of 45 i.e. 31 % of the T1DM patients are HLA-DQ2/DQ8 heterozygotes. The findings of this study are suggest that T1DM with HLA-DQ2 homozygosity are more exposed to CD relative to those with homozygous HLA-DQ8. Supporting this suggestion is the findings of Bao et al, where one third of T1DM patients with homozygous HLA-DQ2 expressed CD-associated transglutaminase autoantibodies [1]. Therefore, understanding the relationship between expression of these HLA genes in T1DM patients and the possibility of developing CD would lead to the identification of key pathways potentially involved in the pathogenesis crosstalk of these diseases, and can be useful in development of preventive measures.

By analyzing the presence of T1DM associated antibody (anti-GAD) and C-peptide in patients

with T1DM and comparing same with T1DM patients having CD, we were able to explore the possible effect of CD on some serological markers in T1DM patients. Antibodies to GAD have well established significance in diagnosis of T1DM even though its role in the pathophysiology of autoimmune diabetes still remains unclear [30]. This enzyme catalyzes the rate-limiting step in the conversion of glutamic acid to gamma-amino butyric acid (GABA), a neurotransmitter in pancreatic islet β-cells as well as in the brain. Although other autoantibodies such as insulin autoantibody (IAA), anti-Zinc transport 8 antibodies (ZnT8A) and so on, have been associated with T1DM, anti-GAD autoantibodies is predominant in 70 - 80 % of T1DM patients and up to 90 % in T1DM children/ adolescents, and has been shown to persist over the years thus characterizing long standing disease duration [31]. Moreover, at the onset of T1DM, approximately 70 – 90 % of patients show positivity for anti-GAD, making it the autoantibody with the highest specificity to T1DM [32]. However, this study recorded just 21 % positivity to anti-GAD in T1DM patients which slightly increased to 31 % in those with CD. The link between anti-GAD antibodies with sensitivity to gluten was investigated by Hadjivassiliou et al where they reported 40 % prevalence of anti-GAD positivity in patients with gluten ataxia [33]. Another important serological marker analysed was C-peptide, a widely used indices for measuring pancreatic β cell function as well as distinguishing between type 1 and type 2 diabetes mellitus. The diagnostic significance of C-peptide is based on its equimolar production with endogenous insulin as it forms the part of pro-insulin cleaved prior to secretion of insulin. Additionally, C-peptide is being excreted at a more constant and slower rate relative to insulin and since insulin production is aberrant in T1DM, many studies have reported low C-peptide levels in T1DM patients [34]. The majority of T1DM patients in this study i.e. 77 % had below normal range values for C-peptide with slightly lower prevalence recorded for those having comorbidity with CD. Considering the absence of significant variation in prevalence of anti-GAD and C-peptide between patients with T1DM only and T1DM patients with CD as observed in this study, the possible effect of CD on pathophysiology of T1DM may occur at early onset of the disease rather than develop during disease progression. To investigate further, this study observed the serum concentration of these T1DM serological markers between the two groups. Despite observing no significant difference in C-peptide levels, the result of this study showed that serum concentration of anti-GAD autoantibodies was significantly higher in T1DM patients with CD. Also, the titer of anti-GAD has been shown to be influenced by gluten sensitivity and the duration of gluten exposure was proposed to increase risk of development of T1DM in patients with gluten sensitive enteropathy [33, 35]. This clearly suggests that CD contributes to anti-GAD seropositivity, which could be due to the central role of autoimmunity in the aetiology of both diseases. The significance of anti-GAD in diagnosis of T1DM has not been directly attributed to its role in the pathophysiology of T1DM, but rather resulted from precipitation of a 65K protein autoantigen with GAD activity in sera of patients with T1DM [36]. However, many explorative studies have tried to unravel the possible mechanism through which GAD can trigger autoimmune diabetes. Pihoker et al, hypothesized that in the case of T1DM, the presentation of GAD to T-cells may unintentionally be the mechanism of initiating the breakdown of immunological tolerance to pancreatic β cells by altering the focus of T-cell response towards generation of pathogenic T-cell response that aggravates autoimmune attack on the pancreatic cells [37]. Interestingly, sensitivity to gluten has been shown to provoke the production of neurological disorder associated GAD antibody [33]. Gluten ataxia mediated inducement of anti-GAD associated ataxia has been previously reported in mice [38], thus highlighting the possible connection between CD and production of anti-GAD antibodies that could trigger the initiation of T1DM.

In conclusion, we can infer from our findings that although T1DM-associated poor glycemic control may be worsened in T1DM patients with CD, deficiency in vitamin D as well as abnormal levels of nephropathic parameters are slightly ameliorated. Also, the detrimental effect of CD on pathophysiology of T1DM may occur at early onset of the disease rather than develop during disease progression. Likewise, the possible connection between CD and production of

anti-GAD antibodies that could trigger the pathogenesis of T1DM was highlighted, suggesting that diagnosis of T1DM should be sufficient to warrant suspicion of subclinical CD especially in children and adolescents. However, future studies aimed towards deciphering the link between CD and production of antibodies to GAD as well as elucidation of molecular pathways through which the autoantibody can trigger the initiation of T1DM would lead to better understanding of the pathogenesis of both disease conditions and provide useful insights towards development of superior therapeutic interventions.

Conclusion

Results indicate major biochemical and genetic changes exist between T1DM only patients compared to those treated for T1DM and CD because their ferritin and vitamin D3 and urea and creatinine levels exhibit important variations. Research findings demonstrate that T1DM + CD patients present higher frequencies of the HLA-DQ2 haplotype along with elevated anti-GAD antibodies which suggests possible immunological connections between these conditions. The existence of CD in T1DM patients leads to worsened glycemic control beside affecting serological tests which monitor autoimmune response activity. The research findings emphasize why medical professionals should examine T1DM patients immediately when they exhibit unexpected metabolic symptoms. Furthermore studies need to investigate how gluten sensitivity interacts with T1DM and CD at the molecular level for developing specific treatments that manage both diseases' combined effects.

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