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# The prevalence of Celiac Disease in Iraqi children and adolescents with type 1 Diabetes Mellitus

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**Abstract**

**Background:** The association of celiac disease with type 1 diabetes mellitus is known worldwide due to shared auto-immunological background. Since celiac disease could present in diabetic patients with non-specific symptoms or asymptomatically, periodic serological screening is necessary for early diagnosis.

**Objective:** To determine the prevalence of celiac disease among children and adolescents with type 1 diabetes mellitus.

**Methods:** A total of 85 patients with type 1 diabetes mellitus (32 males and 53 females) with age range from 1 to 18 years, who were attending the Specialized Center for Endocrinology and Diabetes and Children Welfare at Teaching Hospital , Iraq during the period from November/ 2017 to March /2018. Participants were screened for celiac disease using immunoglobulin A and G anti-gliadin antibody, immunoglobulin A and G tissue transglutaminase (tTG) antibodies. Also, estimation of C-peptide, FPG and HbA1c to diagnosed typ1 diabetes mellitus**.** The results showed that 17 (20.0%) of patients were sero-positive AGA-IgA, and 20(23.53%) were sero-positive for AGA-IgG, whereas the sero-positive patients for tTG-IgA and tTG-IgG were 17 (20.0%), and 21 (24.71%), respectively.

**Conclusion**; There is obvious association of celiac disease among patients with type 1 diabetes mellitus.

**Keywords**: Celiac disease, Anti-gliadin antibodies, Anti-Tissue transglutaminase, type 1 diabetes mellitus.

## INTRODUCTION

Type 1 diabetes Mellitus (T1DM) is an autoimmune disease that results from destruction of pancreatic β cells and consequent insulin deficiency. In addition, it is common in childhood and adolescence, but can occur at any age [1]. It can be associated with other autoimmune disorders such as celiac disease and autoimmune thyroid disease. The associated autoimmune disease(s) may influence the control of diabetes by impairing function of the respective organ [2]. Celiac disease (CD), a common cause of chronic malabsorption in children, is characterized by mucosal damage of the small intestine due to hypersensitivity to gluten containing foods [3]. The association between CD and T1DM has been studied for almost 50 years. Both are autoimmune conditions resulting from a complex interaction between genetic, immunological and environmental factors [4]. The concurrence of two diseases may be explained by a similar genetic background associated with HLA-DQ2, HLA-DQ8 and similar trigger mechanism for autoimmune process [5,6]. The Prevalence of CD in patients with T1DM ranges between 1.3-12% throughout the world and may involve a high proportion of asymptomatic and atypical cases [7]. Several serological tests are used as screening methods for CD such as anti-gliadin, antireticulin, anti-tissue transglutaminase and anti-endomysial antibodies [8]. The main use of these tests in clinical practice is for screening patients with diseases that are associated with CD, yet have atypical or silent forms of CD (e.g. T1DM) without unnecessary intestinal biopsy [9]. The aim of this study was to determine the sero-prevalence of celiac disease in T1DM by using anti-gliadin antibody IgA, IgG, tissue transglutaminase antibody IgA and IgG.

## MATERIAL AND METHODS

A total of 85 patients with type 1 diabetes mellitus (32 males and 53 females) with age range from 1 to 18 years, who were attending the Specialized Center for Endocrinology and Diabetes and Children Welfare at Teaching Hospital, Iraq during the period from November/ 2017 to March /2018. Venous blood samples were obtained from each participant and serum was stored at -20 ºC until testing.

AGA-IgA, AGA-IgG, tTG-IgA and tTG-IgG were determined by enzyme-linked immunoassay (ELISA) (AESKULISA, Germany) in accordance with the manufacturer's instructions. Sera from patients and controls were tested at dilution 1:101, antibody levels were measured by (U/mL). Values more than 12 U/mL were considered positive. Statistical Analysis System- SAS (2012) program was used to study the effect of different study parameters. Chi-square test was used to compare between proportions and unpaired *t*-test was used to compare between means. Estimate of correlation coefficient between variables in this study was also calculated.

## RESULTS

The levels of fasting plasma glucose, HbA1c and C-peptide were significantly different between patients and control subjects (P <0.001; Table 1).

**Table 1 Levels of FBS, C-Peptide and HbA1C for patients and their controls**

| Study Group | No. | Mean±SE | | |
|---|---|---|---|---|
| | | FBS (mg/dl ) | C-Peptide (ng/ml ) | HbA1C (%) |
| Patients | 85 | 218.28±9.13 | 0.462±0.03 | 9.98±0.23 |
| Controls | 30 | 80.87±2.36 | 2.854±0.13 | 4.90±0.11 |
| *t*-test | | 30.659 | 0.191 | 0.795 |
| P value | | 0.0001 | 0.0001 | 0.0001 |

The results also showed significant increase in the levels of Anti gliadin antibody IgA (AGA IgA) and in the levels of Anti gliadin antibody IgG (AGA IgG) among patients with CD and having T1DM in comparison with those having CD but they are not diabetic (control group) (P <0.05; Table 2).

**Table 2 Levels of Anti gliadin antibodies (AGA IgA) and (AGA IgG) for patients and their controls**

| Study Group | No. | Mean±SE | |
|---|---|---|---|
| | | AGA IgA (U/L ) | AGA IgG ( U/L) |
| Patients | 85 | 19.55±4.41 | 30.48±6.83 |
| Controls | 30 | 5.72±0.44 | 5.37±0.34 |
| *t*-test | | 10.750 | 22.852 |
| P value | | 0.05059 | 0.0316 |

Moreover, the results showed that the proportions of patients with CD and T1DM who were sero-positive for AGA IgA, AGA IgG, AtTG-IgA and AtTG-IgG were 20%, 23.53%, 20% and 24.71%, respectively, which were significantly higher than those of control subjects (P <0.01; Table 3) .

Furthermore, serum levels of anti-tissue transglutaminase IgA (AtTG IgA) and of anti-tissue transglutaminase IgG (AtTG IgG) in patients with type 1 diabetes mellitus were higher as compared to control group (P <0.05; Table 4).

**Table 3A Proportions of patients according to presence and absence of Anti gliadins and Anti tissue transglutaminases IgA and IgG**

| Variable | Positive | | Negative | | Chi-Square |
|---|---|---|---|---|---|
| | No. | % | No | % | |
| AGA IgA (No. =85) | 17 | 20.00 | 68 | 80.00 | 13.25 ** |
| AGA IgG (No. =85) | 20 | 23.53 | 65 | 76.47 | 12.07 ** |
| ** (P<0.01). | | | | | |

**Table 3B. Distribution of sample study of patients according to Anti tissue transglutaminase of AtTG IgA and AtTG IgG**

| Variable | Positive | | Negative | | Chi-Square |
|---|---|---|---|---|---|
| | No | % | No | % | |
| AtTG IgA (No. =85) | 17 | 20.00 | 68 | 80.00 | 13.25 ** |
| AtTG IgG (No. =85) | 21 | 24.71 | 64 | 75.329 | 12.33 ** |
| ** (P<0.01). | | | | | |

**Table 4 Serum levels of anti-tissue transglutaminases IgA and IgG for patients and their controls**

| Study Group | No. | Mean±SE | |
|---|---|---|---|
| | | AtTG IgA (U/L) | AtTG IgG (U/L) |
| Patients | 85 | 55.35±16.15 | 32.97±7.84 |
| Controls | 30 | 6.19±0.38 | 5.17±0.32 |
| *t*-test | | 34.025 | 26.224 |
| P value | | 0.0441 | 0.0379 |

## DISCUSSION

A previous study conducted in Iraq [10] showed that the proportion of CD patients with T1DM, who were sero-positive for AGA antibodies, was 30% which is higher than the proportions reported in current study. Other studies which found the mean concentration of screening AGA IgA, IgG was comparable in diabetes patient and healthy control (P<0.01(if results comparable, the will not be significant i.e. P value > 0.05)), while AGA (IgA) was significantly higher in patients than in their controls [2]. On the other hand, these findings are higher than an Egyptian study [11] which reported an AGA level of 4.3%. However, AGA is not disease specific, and some patients with active CD lack these antibodiesIn contrast, patients with diseases other than CD and healthy individual occasionally have elevated levels of AGA-IgA and AGA-IgG [12]. Also, these antibodies disappear rapidly during a gluten-free diet [13].

Similarly, the results of another study [14] revealed that the percentages of patients who were positive for AGA- IgA and AGA-IgG were (17.72%) and (20.15%), respectively, whereas (16.27%) were sero-positive for both IgA and IgG of AGA test. Also other previous Iraqi studies observed the presence of positive IgA and IgG antibodies for gliadin with highly significant differences (P <0.01) with proportions of 81.08% and 36.04%, respectively [15].

Moreover, the proportions reported in current study are higher than those reported in a previous Iraqi study which found 13.3% of patients were sero-positive for both IgA and IgG- AGA [16]. Another study conducted on children with CD in Sudan reported a proportion of 31.3% sero-positive patients for both IgA and IgG-AGA [17] whereas another study reported 17.7% and 20.15% for IgA- AGA and IgG- AGA, respectively [18].

The presence of high titer of AGA whether (IgA or IgG) was proved to be a positive indicator of CD, but it requires further investigation [19]. In AGA test, the sensitivity and specificity of IgA was marginally superior to that of IgG, but IgG testing is particularly useful in the 1% to 2% of patients with CD who have IgA deficiency [20]. Another study also confirmed that IgG- AGA was very sensitive but less specific, and IgA-AGA was less sensitive but more specific. Therefore, it is better to use the combination to give results of a higher detection rate [21]. The AGA test used as a single test in diagnosis of CD is not enough in confirming this disease conclusively, even though the test was positive, but if it might be useful test in monitoring the recovering patients with diet therapy [22]. The AGA test was the best test in wide field to monitor the patient's response to keep the regulator diet system free of gluten.

The measurement of Anti-Gliadin antibodies (AGA) used as a specific test to detect gluten sensitivity in CD [23]. The AGA test appears specific to detect gluten sensitivity rather than celiac disease, since positive AGA was also seen in other diseases and normal people. Thus, the test is of less importance in confirming a diagnosis of celiac disease if used as a single test, but it is good for monitoring diet therapy in established celiac disease [24].

The prevalence of CD among children with T1DM was 8.6% in Iraqi children Diabetics children with CD tend to have stunted growth compared to those without the disease and CD usually appears relatively short after diagnosis of DM in children [25]. Because CD can present either a symptomatically or with nonspecific symptoms in T1DM patients, periodic screening for CD should be part of routine investigations [26].

The association between TIDM and CD was suggested to be due to sharing by seven chromosomes regions between the two diseases and having the same mechanism of autoimmunity-related tissue damage and dietary antigen intolerance [27].

The IgA-tTG test has been known as a research tool since 2000. Its use is not clinically widespread, but would be useful for patients with IgA deficiency to screen them for CD [28]. Previous study [29] found that high levels of IgA-tTG and IgG-tTG antibodies were associated with the grade of mucosal villous atrophy and more severe in clinical cases of CD. In addition, the combination of IgA-tTG and IgG-tTG tests would enable a noninvasive predication of small intestinal villous atrophy with high accuracy, and might reduce the need for biopsy in patients with suspected CD [29]. Tissue transglutaminase represents the predominant, if not the sole characteristic for CD. Usually Anti-Gliadin antibody test was considered less specific and more sensitive than anti-tTG antibodies [23]. Previous study [14] found that, out of 412 Iraqi patients, the proportions of patients who were sero-positive for IgA-tTG and IgG-tTG were 14.56% and 16.75%, respectively. Also, another study [16] reported 13.3% and 15% sero-positivity for IgA-tTG and IgG-tTG, respectively.

Moreover, our results were higher than a previous Egyptian study [30] which found both IgA and IgG-tTG were positive in 4.7% out of 150 suspected patients with CD.

It was shown that the variability of results reported by different studies could be attributed to the manufacturing companies with different serum dilutions and different methods of anti- tTG (e.g. screening and tTG –IgA class or tTG -IgG class) [32]. Also, some authors recommended serological screening at the time of diagnosis of T1DM and annually or biennially, thereafter.

## CONCLUSIONS

Celiac disease (CD) usually appears relatively after a short period from diagnosis of DM in children. Current study showed a 24.71% prevalence of CD among children with T1DM. Moreover, due to the fact that celiac disease can present either asymptomatically or with non-specific symptoms in T1DM patients, periodic screening for celiac disease should be part of routine investigations for those patients.

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