The Detection of Silent Celiac Disease In patients With Type 1 Diabetes Mellitus by the use of Anti Tissue Transglutaminase Antibodies

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Abstract

Objective: Detection the presumptive prevalence of

Methods: One hundred twenty asymptomatic patients

Results : Fourteen out of one hundred twenty (11.66

Conclusion : There is an increased prevalence of IgA antitissue transglutaminase antibodies (11.66 %) in children & adolescent with type 1 diabetes mellitus in comparison with control group.

Keywords:- Diabetes , Celiac disease , Transglutaminase.

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Introduction

Type-1 diabetes mellitus (T1DM) is a chronic autoimmune disorder with varying degrees of insulin deficiency resulting from an immune-mediated destruction of pancreatic β-cells, usually presenting in young individuals & can be associated with other clinical, sub clinical, or potential organ-specific autoimmune diseases. [1]

Celiac disease is a chronic disease causing inflammation of the proximal small intestine that occurs in genetically predisposed individuals when they eat gluten, which is the storage protein in wheat, barley, and rye. [2] Also it can be defined as a unique autoimmune disorder, unique because the environmental precipitant is known & it was previously called celiac sprue, based on the Dutch word *sprue,* which was used to describe a disease similar to tropical sprue that is characterized by diarrhea, emaciation, aphthous stomatitis, and malabsorption. [3] Originally considered a rare malabsorption syndrome of childhood, celiac disease is now recognized as a common condition that may be diagnosed at any age and that affects many organ systems & its main therapy is a gluten-free diet; however, the response to therapy is poor in up to 30% of patients, and dietary nonadherence is the chief cause of persistent or recurrent symptoms, however , Small intestinal adenocarcinoma, refractory sprue, and enteropathy-associated T-cell lymphoma are complications of celiac disease that must be ruled out when alarming symptoms such as abdominal pain, diarrhea, and weight loss develop despite a strict gluten-free diet.[3] A strong association has been observed between celiac disease, generally its silent clinical form, and autoimmune disorders. [4]

Historically, celiac disease (CD) was first described by Dr.Samuel Gee in 1888, who reported poor growth , abnormal stools & abdominal distension as common symptoms in children & in 1950s when the ability to perform peroral mucosal biopsies was established , a

typical small bowel mucosal abnormality in patients with celiac disease was observed characterized by flat appearance of the mucosa , with villous atrophy & hypertrophy of crypts . [5]

Among different types of serological tests for screening Celiac disease, such as anti-gliadin antibodies (AGAs) and antiendomysial IgA antibody (EMA), tissue transglutaminase antibodies (tTGA) has proved to be a very specific indicator to identify subjects with latent Celiac disease & it is well known that clinical Celiac disease represents only the tip of the iceberg , so the subclinical disease is not infrequent in the general population and serological tests such as anti-tissue transglutaminase antibodies can be used as markers for the identification of these asymptomatic individuals & in several studies, its sensitivity was 94% and specificity of 98% compared with biopsy-proven disease & this is important because the treatment of asymptomatic patients with type-1 diabetes mellitus having a gluten- free diet seems to have a positive effect on glycemic control and on the growth & it can prevent osteoporosis and the development of autoimmune diseases. [1]

Patients with selective immunoglobulin (Ig) A deficiency have a 10- to 20-fold increased risk of celiac disease. [6] Conversely , immunoglobulin A (IgA) deficiency is 10 to 15 times more common in patients with celiac disease (CD) than in healthy subjects ; hence, IgA-deficient patients with CD may yield false-negative serology.[7]

Methods

One hundred twenty patients [75 male , 45 female] with type 1 diabetes mellitus who had attended Alrusafa Diabetes & Endocrine centre from 1st of July to 31th of August 2011 were included in this case-control study . Age of patients in this study was ranging from 8 to 18 years & the mean age ± standard deviation was 11.25 ± 2.85 year. All patients were on human insulin and were asymptomatic i.e. none of them had gastrointestinal symptoms suggestive of celiac disease such as diarrhea, abdominal pain, abdominal distention, vomiting or flatulence.

All subjects were serologically screened for the presence of anti-tissue transglutaminase IgA antibodies (anti-tTG antibodies) with Enzyme-Linked Immunosorbent Assay (ELISA) by using commercial kits (ORG 540A) with a cut-off (≥) value of (10 U/ml) . [8] Total IgA was also measured for all using radial immunodiffusion plate (IgA RID , code RK00800) with IgA deficiency to be diagnosed when IgA < 90 mg/dl . [9]

Anti-tissue transglutaminase IgG (ELISA,ORG 540G)was selectively done for patients who were expressing negative anti-tissue transglutaminase IgA with low total IgA levels & a cut-off (≥) value of (10 U/ml) was also considered for anti-tissue transglutaminase IgG .[10]

Results were compared to that obtained from apparently healthy 60 persons with negative personal and family history of diabetes and relatives of diabetic patients were excluded from the study. Their ages ranged from 10 to 23 years & mean age ± standard deviation for them was 15.25 ± 3.85 year .

Inclusion criteria :

1- Patients with type 1 diabetes mellitus .
2- Patients should be asymptomatic for gastrointestinal symptoms that are suggestive of celiac disease .
3- Age less than 19 years (Children & adolescents).[(definition of adolescence) 11]

Exclusion criteria :

1- Patients being already diagnosed or treated for celiac disease .

Results

Table (1): Prevalence of positive anti-tissue transglutaminase IgA antibodies (anti-tTG antibodies) in patients with type 1 diabetes mellitus compared to subjects without diabetes mellitus .

	+VE anti-tTG IgA	**-VE anti-tTG IgA**
Diabetic Patients	14	106
Non Diabetic Patients	1	59

So , 14/120 (11.66 %) diabetic patients had expressed positivity to anti-tissue transglutaminase IgA compared to 1/60 (1.66 %) of non diabetic patients who had expressed such positivity . **P value equals to 0.0221** which is statistically significant.

Table (2): Prevalence of total IgA deficiency in patients with type 1 diabetes mellitus compared to subjects without diabetes mellitus .

	Total IgA deficiency	**Normal total IgA**
Diabetic Patients	3	117
Non Diabetic Patients	0	60

So , 3/120 (2.5 %) diabetic patients had expressed total IgA deficiency whereas all of non diabetic patients were expressing total IgA within the normal range . **P value equals to 0.55** which is statistically not significant.

All of three diabetic patients with total IgA deficiency were not showing positivity to anti-tissue transglutaminase IgG .

Table (3): Significance of gender in patients with type 1 diabetes mellitus with +VE anti-tTG IgA compared to those with -VE anti-tTG IgA.

	+VE anti-tTG IgA	**-VE anti-tTG IgA**
Male	6	69
Female	8	37

P value equals to 0.1426 which is statistically not significant .

Discussion

The presence of significant anti-tissue transglutaminase IgA antibodies (anti-tTG antibodies) in patients with type 1 diabetes mellitus compared to control in this study can be explained in part by the fact that both celiac disease and type 1 diabetes mellitus are associated with the major histocompatibility complex class II antigen DQ2 encoded by the alleles DQA1*501 and DQB1*201, thus providing a common genetic basis for expression of both diseases. [12] Also the presence of a variant of another MHC gene, TNF-α-308A & moreover, it has been hypothesized that MYO9B (myosin IXB) polymorphisms might be involved in the development of both type 1 diabetes mellitus (T1DM) and celiac disease (CD) , presumably through an alteration of the intestinal permeability. [13]

Gluten consumption might be a shared causative factor for both diseases, as confirmed by the possible concomitant onset of both disorders & moreover , withdrawal of gluten in patients with celiac disease (CD) diagnosis without type 1 diabetes mellitus (T1DM) , is rarely associated with the appearance of immune markers of type 1 diabetes mellitus (T1DM) and the development of type 1 diabetes mellitus (T1DM) & the hypothesis that viral infections would have a role in the pathogenesis of both disorders has been strengthened by the demonstration that rotavirus, responsible for gastrointestinal infections in infancy, has been recently recognized as one of the pathogenic factors of CD . [13]

The prevalence of anti-tissue transglutaminase IgA antibodies (anti-tTG antibodies) in patients with type 1 diabetes mellitus in our study was 11.66 % (**P value equals to 0.0221** & it is considered to be statistically significant) compared to an Indian study [1] published in 2009 which was showing just slight lower prevalence of 8 % ; but , a Turkish study [14] (performed during 2006-2007) for 48 diabetic children was showing that 10 patients (20.8%) were seropositive for celiac disease using anti-tissue transglutaminase IgA & IgG antibodies ,

whereas an Egyptian study [15] had revealed a prevalence of 5.48 % for anti-tissue transglutaminase antibodies among Egyptian type 1 diabetic children . Generally speaking , Prevalence of coeliac disease (CD) in patients with diabetes mellitus type 1 (DM) has been estimated from 1.7 to 16.4% in different populations . [16] The different rates reported between these studies may be due to a number of factors including methodological reasons (differences in type of antibody used for screening), the size and age of the cohort, and possible genuine underlying geographic differences that may be explained by genetic or environmental factors. [17 , 18]

In the present study , the non significance of expressing total IgA deficiency in diabetic patients of 2.5 % compared to nil in non diabetics (**P value equals to 0.55)** can be supported by the fact that although type 1 diabetes mellitus (T1DM) and selective IgA deficiency are both associated with the presence of non-Asp amino acids at position 57 of the HLA DQ beta chain, the frequency of this immunodeficiency in adult type 1 diabetes mellitus (T1DM) patients is not significantly increased . [19]

Consequently , comparing our finding regarding total IgA deficiency in patients with type 1 diabetes mellitus (T1DM) with obtained results in the previously mentioned Indian study [1] , we will find 4% prevalence of total IgA deficiency in patients with type 1 diabetes mellitus (T1DM) but with no statistical significance
($P > 0.05$) , also an Iranian study [20] publishd in 2010 had revealed 0.7% prevalence of total IgA deficiency in 300 Iranian patients with type 1 diabetes mellitus (T1DM) it had been showen a significantly higher prevalence of immunoglobulin A deficiency among type 1 diabetes mellitus (DM1) patients of (5.3%).[21]

So , an increased prevalence of immunoglobulin (Ig) A deficiency has been documented in a number of autoimmune diseases; however, its association with type 1 diabetes mellitus (DM1) is a subject of debate. [20]

Finally , taking into account gender distribution between positive & negative anti-tissue transglutaminase IgA antibodies (anti-tTG antibodies) in patients with type 1 diabetes mellitus in the present study , p value was not significant ; again the same non significant results had been obtained for gender distribution in the previously mentioned Indian study [1] & also to an Egyptian study [18]

Conclusion

There is an increased prevalence of IgA antitissue transglutaminase antibodies(11.66 %) in children & adolescent with type 1 diabetes mellitus in comparsion to general population , which suggests the need to use this method as an effective first-line test in the screening of celiac disease in those patients .

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