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Evaluation of Anti-transglutaminase Antibodies in Iraqi Patients with Celiac Disease

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A B S T R A C T

Anti-tissue antibodies have high specificity for celiac disease but measurements are limited, a substrate that is expensive, and of limited availability and ethical acceptance. Tissue transglutaminase has recently been identified as the endomysial autoantigen in celiac disease. To examine the validity of serum tissue transglutaminase antibody levels in patients with celiac disease and to assess their sensitivity and specificity against standard serological tests. Serum IgA anti-tissue transglutaminase antibody titres (measured by ELISA), IgG anti-tissue transglutaminase antibody titres (measured by a commercial ELISAwere determined in 168 untreated patients celiac disease collected from Baghdad Teaching Hospital,Iraq. patients with untreated celiac disease were positive for IgG and IgA anti-tissue transglutaminase antibodies. A bout eighty-two per cent of coeliac patients were anti-tissue transglutaminase antibody negative. Twenty eight of 168 patients had high titres of anti-tissue transglutaminase antibody (percentage 17.2%). the present results demonstrated the levels of IgA anti-tissue transglutaminase antibodies in the diagnosis of celiac disease. The ELISA for IgA anti-tissue transglutaminase antibodies is quantitative and easy to perform and is a valid alternative to indirect immunofluorescence for anti-tissue antibodies in screening for suspected celiac disease that's mean it can be used as diagnostic marker for celiac disease.

Introduction

Celiac disease (CD) is a digestive disease that damages the small intestine and interferes with absorption of nutrients from food. People who have celiac disease cannot tolerate gluten, a protein in wheat, rye, and barley. Gluten is found mainly in foods but may also be found in everyday products such as medicines, vitamins, and lip balms (Yasemin Bayrama; 2015). CD is one of the most common causes of chronic malabsorption (Di Sabatino, 2009). This results from injury to the small intestine with loss of absorptive surface area, reduction of digestive enzymes, and consequential impaired absorption of micronutrients such as fat-soluble vitamins, iron, and potentially B 12 and folic acid (Reilly, 2012). In addition, the inflammation exacerbates symptoms of malabsorption by causing net secretion of fluid that can result

in diarrhea. The failure of absorption of adequate calories leads to weight loss, and the malabsorption results in abdominal pain and bloating (Reilly, 2012). These are common symptoms associated with CD (Rostom, 2006).

Celiac Disease may present in many ways (NIH, 2014). Currently, active case-finding (serologic testing for CD in patients with symptoms or conditions closely associated with CD) is the favored strategy to increase detection of CD (Reilly, 2012). Active case-finding may increase detection of CD among patients with symptoms attending a primary-care office, although this strategy is insufficient to detect most patients with CD (NIH, 2014). There is no consensus regarding which symptoms, laboratory abnormalities, and / or associated diseases require evaluation for CD. The frequency of CD in common clinical scenarios varies from modestly elevated, such as irritable bowel syndrome, to substantially elevated, such as unexplained iron-deficiency anemia

The complexity of deciding who to test is exemplified by patients with dyspepsia. The prevalence of biopsy-proven CD in patients with dyspepsia is 1 %, similar to that of the general population (Karimi S, Mohammadkhani, 2013), and therefore systematic screening for CD is not recommended based on disease prevalence alone. However, treatment for dyspepsia can be a clinical challenge (Jayden, 2014) and dyspepsia as a symptom of CD will readily respond to the gluten-free diet (GFD) (Akbari, 2006). Thus, mucosal biopsies of the duodenum should be considered in patients with dyspepsia who undergo investigation with upper endoscopy because of persistent symptoms despite initial therapy, are aged > 55 years old, and / or present alarm symptoms (e.g., weight loss or clinical evidence of anemia) (Jayden, 2014).

Anti-transglutaminase antibodies (ATA) are autoantibodies against the transglutaminase protein. Antibodies serve an important role in the immune system by detecting cells and substances that the rest of the immune system then eliminates. These cells and substance can be foreign (for example, viruses) and also can be produced by the body (for example, cancer cells). Antibodies against the body's own products are called autoantibodies. Autoantibodies can sometimes errantly be directed against healthy portions of the organism, causing autoimmune diseases. ATA can be classified according to 2 different schemes: transglutaminase isoform and immunoglobulin reactivity subclass (IgA, IgG) toward transglutaminases. Most attention to anti-transglutaminase antibodies is given with respect to coeliac disease (Hill, 2006). In study done on children published in 2007 demonstrated that the level of ATA in correlates with the scalar Marsh score for the disease in the same patient *(*Donaldson, 2007). High levels (titers) of ATA are found in almost all instances of coeliac disease (NIH, 2014). Given the association of ATA with coeliac disease, and the prevalence of the latter, it is estimated that ~1% of the population have potentially pathogenic levels of ATA.

The present study aimed to assess the levels of anti tissue transglutaminase in Iraqi patients with celiac disease.

Subjects and Methods

This study done in Baghdad Teaching Hospital in the period from April to August 2015. A total (163) subjects include in this study with age range (less 1 year to 30 year). All patients were referred for evaluation because of gastrointestinal or systemic complaints suggestive of CD, family history of GSE, recent diagnosis of type 1 DM or

other associated autoimmune disease, or having Down syndrome. The medical history was taken, body weight and height were measured and body mass index (BMI) was calculated (the present study exclude the obese subjects). Serum Anti-huTransG IgA was determine by using ELISA technique (Generic Assay GmbH, Germany). As well as, human Anti-huTransG IgG determine by ELISA kit ((Generic Assay GmbH, Germany).

Statistical Analysis

Statistical analysis was performed using SPSS-21 (Statistical Packages for Social Sciences- version 21). Unpaired t-test was used to assess significant difference between means. $P < 0.05$ was considered statistically significant.

Results and Discussion

Table (1) show the percentage of patients with positive Antitissue IgA Ab and Antitissue IgG Ab and the patients with positive results for each parameters.

There was a significant difference between the number of patients with positive results for IgA when compare to negative subjects (135,82.8% vs. 28,17.2%, respectively), as shown in figure (1).

As well as, figure (1) also shown that there was a significant difference between the number of patients with positive results for IgG when compare to negative subjects (135,82.8% vs. 28,17.2%, respectively).

When compare between subjects with positive results for each parameters (IgA & IgG) with negative results also found significant difference between them (146, 89.6% vs. 17,10.4%, respectively).

There was a highly significant difference when compare between patients and control subjects group ($p<0.01$), as shown in table (2).

In the current study also found that there was a highly significant difference when compare between patients and control groups, Table (3).

The guidelines of the European and North American societies for gastroenterology require a biopsy for diagnosis of CD (Report 2001, Hill ID,2005) However, because of the inconvenience and high cost associated with jejuna biopsy and the high prevalence of CD in the general population, less invasive procedures are required (Bürgin-Wolff A, 2013.). The detection of auto-antibodies is often used as a first-line test to identify individuals who might require a duodenal biopsy.

The current study designed to evaluate the anti-transglutaminase antibodies in two classes which are IgA and IgG in celiac disease in Iraqi patients. The present study found that both the Antitissue IgG Ab and the Antitissue IgA Ab significantly elevated in patients.

In a previous study observed that the IgG-tTG response showed delayed kinetics compared with the IgA-tTG response in CD children who were subjected to gluten challenge, and it is possible that a larger amount of dietary gluten is needed to elicit a detectable IgG-tTG response(Hansson, T., 2002.). The disparity in the isotypic composition of the anti-tTG response observed in our study might reflect in part individual variations in gluten intake.

Table.1 The Different Age Groups and the Positive Percentage of Antitissue IgA and IgG

Age Group	Antitissue IgA Ab Positive	Antitissue IgG Ab Positive	Antitissue IgA Ab & IgG Positive
Group 1 : less than 1 yr	0 (0.0%)	1 (3.6%)	0 (0.0%)
Group 2 : 1-5 yr	3 (10.7%)	4 (14.3%)	1 (5.9%)
Group 3 : 5-10 yr	8 (28.6%)	9 (32.1%)	5 (29.4%)
Group 4 : 10-15yr	8 (28.6%)	6 (21.4%)	4 (23.5%)
Group 5 : 15-20 yr	1 (3.6%)	1 (3.6%)	0 (0.0%)
Group 6 : 20-25 yr	3 (10.7%)	3 (10.7%)	3 (17.6%)
Group 7 : more than 25 yr	5 (17.9%)	4 (14.3%)	4 (23.5%)
Total	28 (100%)	28 (100%)	17 (100%)

Table.2 The Paired T-test between the Anti-tissue IgA Ab of Patients and Controls

Parameter	Sample size	Mean	Standard deviation	P.value
Patients Antitissue IgA Ab	20	201.475	165.5421	0.0001*
Controls Antitissue IgA Ab	20	2.505	2.0459	

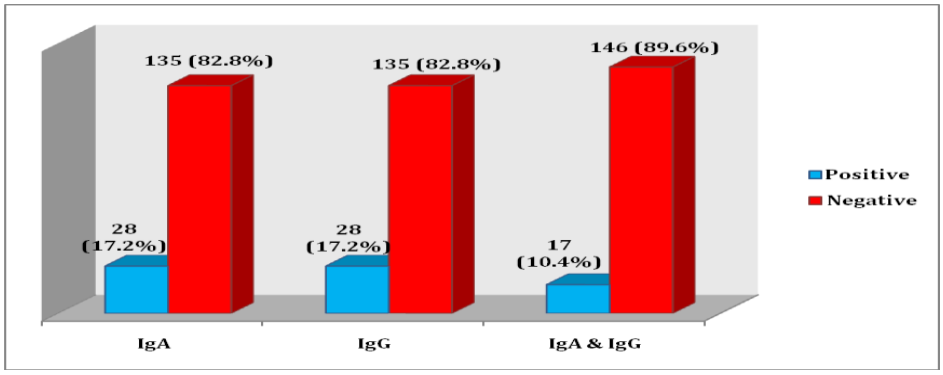
*P.value <0.01 is significant

Table.3 The paired T-test between the Antitissue IgG Ab of patients and controls

Parameter	Sample size	Mean	Standard deviation	P.value
Patients Antitissue IgG Ab	20	161.190	150.2088	0.0001*
Controls Antitissue IgG Ab	20	2.175	1.8450	

*P.value <0.01 is significant

Figure.1 The Positive and Negative Percentage of Anti-tissue IgA and IgG



Moreover, IgA-tTG seems to be directed mainly against conformational tTG-epitopes (Halttunen, 2015.), and it is possible that IgG-tTG is directed against the same epitopes. Hence, a competition between IgA-tTG and IgG-tTG might take place, and

this competition would favor antibodies with a high avidity for tTG. The extent to which IgA-tTG and IgG-tTG might differ with respect to binding avidity and epitope specificity for tTG has not been investigated, and the clinical implications of the presence of IgG-tTG in patients with CD remain to be resolved in future studies.

Hill PG suggested that CD is a multisystem disorder and the adult or child patient may initially present to a wide range of clinical specialties. The concept of the 'celiac iceberg' has been used to emphasize that many cases currently remain undiagnosed. The identification of tissue transglutaminase (TGA)-2 as the antigen against which the autoantibodies are directed has led to a greater understanding of the pathogenesis of CD and to the development of improved serological tests (Hill, 2006).

Other study reported that IgA anti-tTG are currently the most recommended tests for CD while the patient is on a gluten-containing diet. Although the reported sensitivity (+/- 93.9%) and specificity (96.5%) of the second generation of IgA anti-tTG assays are seemed to be good, there are also controversial data about the sensitivity and specificity of IgA anti-tTG in the clinical practice.(Geboes, 2009)

In conclusion, the study revealed that physicians should be used IgG and IgA anti-tTG in the diagnosis of CD.

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