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Association of Autoimmune Thyroiditis and Type 1 Diabetes Mellitus With Severity of Children with Celiac Disease

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Abstract

Purposes of study: analysis and measurement of incidence and association between autoimmune thyroiditis(AIT) and type 1 Diabetes mellitus(T1DM) with clinical and serological severity of patients with Celiac disease.

Design and Methods: This is prospective study, All children (107 children with 41 male and 66 female) with celiac disease are admitted and follow up in Hospital. Age groups (1-12 years) are arranged into two groups (1-6 and 7-12 years old). The celiac disease are divided into: Group1= 25-50 IU/ml, Group2 = 50-100 IU/ml, Group3 >100 IU/ml. All patients with celiac disease are follow up for AIT and type 1 T1DM.

Results: (107) patients with celiac disease, mean age is 6.78±2.85, median age is 8, and female :male ratio are 1.6:1. All celiac patients are divided into: group 1 (43 patients), group 2 (50 patients), and group 3 (14 patients). Incidence of T1DM in all patients is 8.4% while AIT 2.8% . T1DM incidence in group 2 is 3.7% and in group 3 is 12.3%. But AIT incidence in group 3 is 4.6%. All cases with AIT have hypothyroidism with TSH > 100 μU/ml. All diabetic patients have random blood sugar > 450 mg/dl. Age group are divided into two groups, 1-6 and 7-12 years old. Incidence of T1DM are 6.25% and 11.6% in these two age groups respectively, while AIT is 7% in age group 7-12 years. The association between celiac patients groups with T1DM and AIT is insignificant association ((P value is 0.265 and 0.717 respectively). Also age groups have no significant association with T1DM and AIT ((P value is 0.48 and 0.062 respectively) .

Conclusion: follow up of celiac disease is important step for diagnosis AIT and T1DM . These two autoimmune diseases are increasing especially when there high concentration of IgA anti-tissue transglutaminase level (>100 IU/ml) and advanced children age group . AIT may presented initially with hypothyroidism.

***Key words**: Celiac disease, autoimmune thyroiditis, type 1 diabetes mellitus.*

Introduction:

Celiac disease is an initially described as bowel disease in 1st century A.D. It is also called gluten sensitive enteropathy or celiac sprue [(1)] .

Celiac disease is intestinal autoimmune disease which is triggered by gluten ingestion in genetically liable persons. The main distinctive features of celiac disease are systemic symptoms , serologically autoimmune antibodies ,and lastly, there is genetic association [(2)] .

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Sex distribution have also different rates of disease involvement , female is increased 1.5-2 folds in compare to male[(3)] .

Since, there is commonly unclear and wide variation clinical symptoms of celiac disease and so the real prevalence of this disease is not accurate[(4-6)] . Consequently, patients with celiac disease is underdiagnosed in about 90%[(7-9)] .

Gastrointestinal symptoms of celiac disease are malabsorption with diarrhea and subsequently, it is leading to weight loss. The intestinal biopsy shows mucosal inflammation of proximal small bowel with variable level of inflammatory extension to jejunum and

ileum [10].

The prevalence distribution of this disease is 1%-2% in North and South America, North Africa and Middle East with first suggestion in the same degree in Asian population [11]. Family history of 1st degree people is also rising the incidence of celiac disease to about 10%-15% [12].

European society of pediatric gastroenterology, hepatology and nutrition (ESPGHAN) have diagnostic principles and recommendation for diagnosis of celiac disease.

Celiac diagnostic criteria is yet depending on intestinal biopsy that have typical findings with positive response to gluten free diet but further biopsies (2nd and 3rd) are done only when first biopsy findings is unclear and/or gluten free diet ingestion is not changing clinical outcome of patients. Most recent diagnostic criteria (ESPGHAN-2012) is depending on characteristic symptoms, titer level of transglutaminase antibodies (ten times greater than upper normal value), and presence of associated HLA-genotype[13].

Regarding serology, patients is testing by serum IgA anti-tissue transglutaminase antibodies[14] .if they have IgA antibodies deficiency, both serum IgG anti-tissue transglutaminase and IgG anti-deaminated gliadin antibodies can use [15].

Incidence of celiac disease is increasing in previous fifty years and the mechanism of these changes is not completely identified but it might be related mostly to environmental factors in addition to effect of genetic abnormalities[16].

Type 1 diabetes mellitus (T1DM) is common endocrine disease that is appearing in children adolescence age group. T1DM is a result as outcome of defect in patient genes, immunity, and environmental stimulation factors, and these factors result in stimulation of T-cell autoimmunity against beta cells of pancreas [17].

Thus, T1DM is resulting from decrease insulin secretion from pancreas, and it is associated frequent urination and thirst. Diagnostic standardization of world health organization standardization of T1DM are fasting blood glucose ≥ 7 mmol/L or blood glucose ≥ 11.1 mmoI/L in addition to diabetes mellitus symptoms or when oral glucose tolerance test is resulting two hour blood glucose ≥ 11.1 mmoI/L. [18].

The T1DM is rising in incidence and it is risk could be increase to double level in children by 2020[19].

T1DM are associated other autoimmune diseases and so with firstly autoimmune thyroiditis and then celiac disease[20].

Autoimmune thyroiditis (AIT) is a widespread autoimmune disorder, it is affecting 0.2% and 2% of men and women respectively[21].

Autoimmune hypothyroidism is a common etiology for acquired hypothyroidism that presenting from children to adult age group, AIT prevalence is 1%-2% and female is four folds than male[22] . Autoimmune hypothyroidism is commonly associated with systemic lupus erythematous, celiac disease, and other diseases[23].

Antithyroglobulin and antithyroid peroxidase autoantibodies is found in about 60% and 95% respectively in patients with both diffuse goiter and hypothyroidism or one of them [24].

Aim of study is to evaluate incidence and association between autoimmune thyroiditis and type 1 Diabetes mellitus with clinical and serological severity of patients with Celiac disease.

Materials and Method

This is prospective study, All children (107 children with 41 male and 66 female) with celiac disease are admitted and follow up in Babylon teaching hospital for gynecology and pediatrics, in period between April/2017 to February/2019. Age group involved is 1-12 years old that arranged into two groups (1-6 and 7-12 years old) . The diagnosis of celiac disease is depending on symptoms, serum anti-tissue transglutaminase IgA (TTGA) and intestinal biopsy. The celiac disease are divided into three groups according to concentration of IgA anti-tissue transglutaminase : (1) Group1= 25-50 IU/ml; (2) Group2 = 50-100 IU/ml; (3) Group3 >100 IU/ml .

All patients with celiac disease are follow up for AIT and T1DM .

T1DM is diagnosis by random blood sugar with clinical symptoms and fasting blood sugar. Also, autoimmune thyroiditis is follow up with antithyroglobulin and antithyroid peroxidase autoantibodies in addition to

presence of goiter with other thyroid disorder symptoms. Then, if the children has AIT, we do thyroid serology for thyroid stimulating hormone (TSH) and free thyroxine (FT4) hormones.

In Hospital laboratory, the serology of TSH and FT4 is measured with cobas e 411 analyzer . anti-tissue transglutaminase IgA, antithyroid peroxidase antibodies, and antithyroglubin antibodies measured by Chorus trio machine .

Laboratory normal reference for following data are : FT4: 10-35 pmol/L, TSH: 0.25-5 µU/ml, anti-tissue transglutaminase IgA titer < 12 IU/ml (negative) and 12-18 IU/ml (equivocal), antithyroid peroxidase antibodies titer < 35 IU/ml, antithyroglubin antibodies titer : 2.6-25 ng/ml.

SPSS version 22 program was using for Statistical evaluation. Mean ± SD and median are represented the continuous variable. Pearson´s chi square (X2) and Fisher's Exact Test are assessed the association between categorical variables, and Significant P value is ≤ 0.05 .

Results

107 patients are diagnosis with celiac disease, mean age is 6.78±2.85, median age is 8, and female :male ratio are 1.6 : 1.

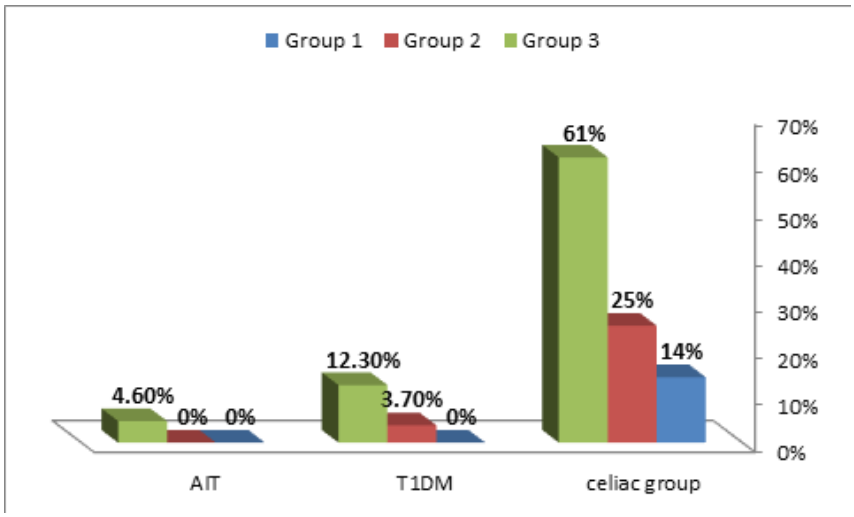
All patients with celiac disease are divided according to level of TTGA into group 1 (43 patients), group 2 (50 patients), and group 3 (14 patients).

During period of follow up of those patients, the incidence of T1DM in all patients is 8.4% while AIT 2.8% . T1DM incidence in group 2 is 3.7% and in group 3 is 12.3%. But AIT incidence in group 3 is 4.6% as in table1 and Fig.1.

Table 1 : Compare incidence and assiciation between autoimmune thyroiditis and type 1 diabetes mellitus according to severity of celiac disease.

Celiac disease				
	Group 1 (mild cases)	**Group 2 (moderate cases)**	**Group 3 (sever cases)**	
IgA anti-tissue transglutaminase concentration	**25-50 IU/ml**	**50-100 IU/ml**	**> 100 IU/ml**	***P value**
cases N(% from total patients)	15 (14%)	27(25%)	65(61%)	
T1DM N(% from each group)	0	1(3.7%)	8(12.3%)	0.265
AIT N(% from each group)	0	0	3(4.6%)	0.717

*Fisher exact test



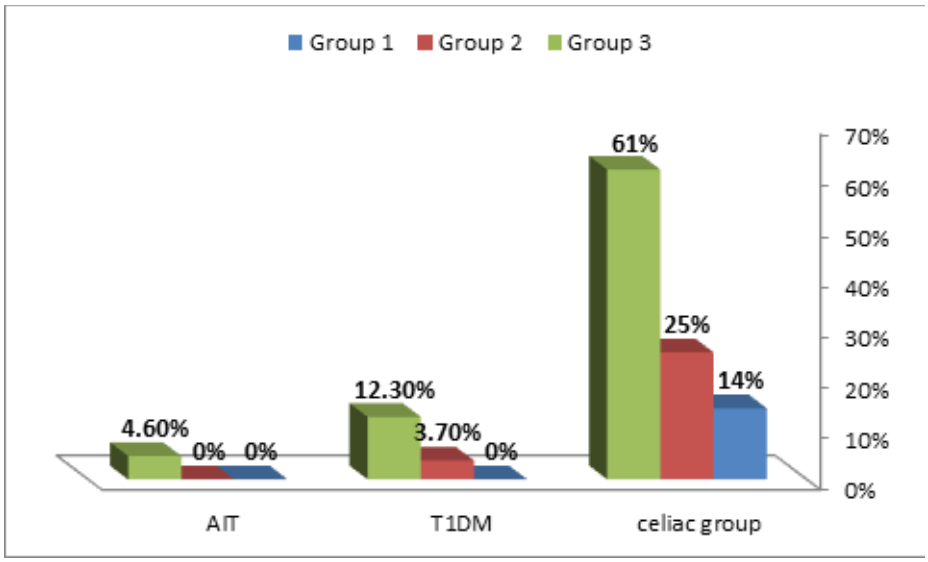


Fig. 1: Distribution of autoimmune thyroiditis and type 1 diabetes mellitus in patients with celiac disease.

all cases with AIT have hypothyroidism with TSH > 100 µU/ml. All diabetic patients have random blood sugar > 450 mg/dl.

Also, age group are divided into two groups, 1-6 and 7-12 years old. Incidence of T1DM are 6.25% and 11.6% in these two age groups respectively, while AIT is 7% in age group 7-12 years as shown in table 2.

Table 2 : Compare incidence and association between autoimmune thyroiditis and type 1 diabetes mellitus according to age group.

Age group			
	1-6 years	7-12 years	*P value
Cases N(% from total patients)	64 (60%)	43 (40%)	
T1DM N(% from each group)	4 (6.25%)	5(11.6%)	0.48
AIT N(% from each group)	0	3(7%)	0.062

*Fisher exact test

The association between celiac groups with T1DM and AIT is insignificant association (*(P* value is 0.265 and 0.717 respectively). Also age groups have no significant association with T1DM and AIT (*(P* value is 0.48 and 0.062 respectively) .

Discussion

In this study, we study association of AIT and T1DM in patients with originally diagnosis as celiac disease , all these diseases have an autoimmune origin, and many studies support their relationship.

Celiac disease is commonly associated with T1DM, AIT, and Sjogren's syndrome[25] .

Kahaly et al indicated in their research that type 1 diabetic patients are fifty percentage that may progress to autoimmune thyroiditis and forty percentage are presented with celiac disease [26] .

This present study is accomplished in hospitalized children, mean age is 6.78 predominant female (female : male ratio is 1.6 : 1). Antonella el at. [27] study was done in 324 children that had always celiac disease, mean age is 6.6 years old, and female to male ratio is 2:1.

Our study shows percentage of T1DM (8.4%) is more than autoimmune thyroiditis (2.8%) . Antonella el at. [27] and Collin et al. [28] exhibited that autoimmune thyroiditis were found 10.5% and 3.5% respectively in patients with celiac disease.

Also, T1DM was diagnosis about 3.5%-10% in patients having celiac disease[29-31] .

Study of PEKKA et al. [32] was diagnosis of both autoimmune thyroid disease and T1DM with equal evidence (2%-5%) in celiac disease.

High IgA anti-tissue transglutaminase level (>100 IU/ml) in group 3 has more (in compared to other groups) association to develop T1DM and AIT, but their association is not reach to significant level *(P* value is 0.265 and 0.717 respectively).

Age factor in celiac disease responsible for prediction of developing autoimmune diseases, rather than the period of gluten ingestion as a registered by authors[33]

Two age groups in present study are insignificant associated with AIT and T1DM in this present study, but age group 7-12 years are higher frequency with AIT(7%)in compare to age group 1-6 years (0%), similar study of Giuseppina et al. [34] is 4.3% for age group < 6 years in compare to 27.7% age group > 6 years old.

Also,T1DM is occurring in both age groups (6.25% and 11.6% respectively) that have celiac disease, and as known that T1DM is common disease in both children and teenager [35] .

In conclusion, follow up of celiac disease is important step for diagnosis AIT and T1DM . These two autoimmune diseases are increasing especially when there high concentration of IgA anti-tissue transglutaminase level (>100 IU/ml) and advanced children age group. AIT may presented initially with hypothyroidism.

Ethical Clearance: The Research Ethical Committee at scientific research by ethical approval of both environmental and health and higher education and scientific research ministries in Iraq

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