

The prevalence of thyroiditis and celiac disease in a sample of type one diabetic iraqi children.

**Dr.Noaman Abdulateef Abdulrazzaq,FICMS,DCpath,MBChB*

**Dr.Mohammed Essa,FICMS,MBChB*

**Dr.Abdulmotaleb Abdulkareem Mostafa,D.R.D.Reh.,MBChB*

Abstract

The prevalence of Celiac disease(CD), Thyroiditis in 120 Iraqi child and adolescence with type one diabetes (T1DM), age 2-18 year old, with 67 male (55.83%) and 53 female (44.16%), selected from Almansor Hospital for children, their serum samples were analyzed in the immunology and biochemistry departments of the Central public health laboratory in Baghdad to detect any significant antibodies titer related to T1DM, CD, and thyroiditis. The percents of autoimmune T1DM, CD, Thyroiditis were found to be 70.83%, 15.83%, 9.16% respectively. Celiac disease (CD) is one of the most frequent autoimmune disorders occurring in T1DM, the clinical presentation of CD in T1DM is classified as Symptomless in approximately half of cases, but a more accurate analysis often discloses a wide array of symptoms suggestive of CD. The thyroid is a frequent target of autoimmune problem, Hashimoto's thyroiditis and Graves' disease are two of the most common autoimmune diseases. Recently Autoimmune polyendocrine Syndromes (APS), also referred to as Autoimmune Polyglandular Syndromes, are a family of diseases that involve several endocrine organs becoming deficient as a result of the failure of the immune system to properly distinguish between self and enemy. Patients with APS are diagnosed based on the co-occurrence of several diseases, such as T1DM disease, thyroiditis, CD, and others which taken together indicate that there has been a large scale failure of the immune system. The three conditions shows the same genetic background. screening for CD, thyroiditis, should be performed in all T1DM patients by means of tissue transglutaminase auto-Abs (anti-tTG auto-Abs), anti gliadin autoantibody (antiGL Abs), antithyroid peroxidase autoantibody (antiTPO), antithyroglobulin autoantibody (antiTG). while, T1DM autoAb (anti-insulin, anti-glutamic acid-decarboxylase 'anti-GAD', anti-pancrease, anti-tyrosine-phosphatase autoantibody 'anti-IA2'). T3, T4, & TSH measurements revealed abnormal values in 24 samples where only three of them showing increased antiTG, antiTPO antibodies.

Objectives; To shed a light on the prevalence of thyroiditis and celiac disease in 120 diabetic type one Iraqi children. **SETTING**; Central public health laboratory (CPHL)-Iraqi ministry of Health. **Patients & Methods**; 120 diabetic type 1 child and young adolescents from Almansor hospital (aged 2-18 year with 67 male and 53 female) were screened for DM, CD, Thyroiditis autoantibodies titers using ELISA-system except for antipancrease autoantibody in which we used IFAT principal. T3, T4, TSH were measured in all samples using radioimmuno assay principal through gamma counter system. **Results**; From 120, only 91 samples shows positive autoantibodies (62 of DM, 13 of both DM and CD, 9 of both DM and Thyroiditis, one for DM/CD and Thyroiditis, 5 for CD only, and in the last sample we found only autoantibodies concerned with thyroiditis). The remaining 29 cases doesn't explore any antibodies. **Conclusion**; There are an increased association of autoimmune disorders among T1DM.

KEY WORDS: POLYGLANDULAR AUTIMMUNE SYNDROM,TYPE ONE DIABETES MELLITUS,CELIAC DISEASE,THYROIDITIS,AUTANTIBODIES.

Introduction

Polyglandular autoimmune syndrome is a rare disorder characterized by the association of two or more organ-specific autoimmune disorders. It is estimated that about one-fourth of patients with a single organ-specific autoimmune disease may have or develop other autoimmune diseases. Polyglandular autoimmune syndromes (PAS) are a group of disorders characterized by endocrine tissue destruction, which causes multiple glands to malfunction. PAS occur when the immune system attacks the endocrine glands and cripples hormone production. Genetics also play a role in determining who develops PAS (1). Type 1 diabetes, a common autoimmune endocrine disease in children and adolescents, is frequently associated with other autoimmune diseases and autoantibodies (2). The most prevalent autoimmune disease associated with type 1 diabetes is Hashimoto thyroiditis, its prevalence varies from 8 to 50% depending on the age, sex, and ethnic origin of the subjects (3-6). Because of this high prevalence, most investigators recommend screening children and adolescents with type 1 diabetes for autoimmune thyroid disease (7-10). Celiac disease coexists with type 1 diabetes less frequently than does Hashimoto thyroiditis. Its prevalence in children and adolescents with type 1 diabetes ranges from 3 to 8% (11-16), a much higher prevalence than that found in the general population. Thus routine screening of type 1 diabetes patients for celiac disease is also recommended (17).

Types of PAS : There are four different kinds of PAS. They are distinguished by which endocrine failures are present when a diagnosis is

made. *Type 1 PAS; usually affects children around the age of 10 to 12. It is a rare genetic condition that usually starts with chronic yeast infections and progresses to include the parathyroid and adrenal glands, resulting in hypoparathyroidism and Addison's disease. Other related autoimmune disorders can develop over the years.

*Type 2 PAS; occurs in adults, with women being three times more likely than men to develop it. It usually starts with adrenal gland insufficiency and progresses to include the thyroid (hypothyroidism) and the pancreas (Type 1 diabetes). Pernicious anemia also frequently accompanies PAS 2, as well as other disorders such as vitiligo, alopecia, myasthenia gravis, rheumatoid arthritis and several other autoimmune conditions. *Type 3 PAS; also mainly affects women in their 30's. It typically starts with thyroid dysfunction and progresses to other autoimmune disorders including diabetes, pernicious anemia, celiac disease and many of the same conditions that occur in PAS 1 and 2. It doesn't typically include adrenal gland malfunction(18).

*Type 4 PAS; usually have two or more autoimmune endocrine diseases that don't follow the typical pattern for the other types of PAS. For instance, a person may have type 1 diabetes first and then go on to develop celiac disease without adrenal or thyroid involvement(19).

The purpose of this study was to explore the prevalence of autoimmune thyroiditis and celiac diseases among type one diabetic children.

Patients & Methods

120 diabetic patients,53 female and 67 male , from Alyarmouk endocrinology

unite and Almansore pediatric hospital with an age group range from 2-18 year, was enrolled in this study between jan 2011-jan 2012 , all the patients presenting with type1 diabetes to the outpatient clinic or to diabetic ward were investigated and proved to have diabetes mellitus type 1. all subjects were investigated for T3(60-160 nmol/L) ,T4(Euthyroid: 0.17-4.04;hyperthy:≤0.15; Hypothy:≥5mlU/L), and with a normal reference for TSH Up to 100 U/ml using gamma counter instrument with a radioimmune assay(RIA) principal.

All lab. measurements were performed in the central public health lab. by clinical chemistry and immunology units including blood sugar rechecking for verification. Tests results and interpretation all done under supervision of senior doctors specialist Using enzyme linked immunosorbent assay(ELISA) principal we were investigate those children as follows ; 1. To detect autoimmune DMT1; anti-insulin, anti-IA2 (tyrosine phosphatase),and anti-glutamic acid decarboxylase (Anti-GAD) antibodies with a normal reference ranges of Up to 50 U/ml, Up to 10 U/ml, Up to 10 U/ml respectively). 2.For Thyroiditis; anti-thyroglobulin antibody (Anti-TG), anti-thyroid peroxidase antibody (Anti-TPO) with a

Sex distribution among T1DM shows no significant relationship to these disorders (tabl.4) .on the contrary age distribution have such relationship in that there are only 28 child have a mean age of 6.6 year below ten year

normal range up to 20 AU for both of them. 3.Anti- gliadin antibody (ANTI-GL; IgA , IgG) with a normale ranges up to 50 AU, and Tissue transglutaminas antibody (Anti-t TG; IgA,IgG) with normal range up to 20 AU, both for detection celiac disease(CD).

4.Anti-pancrease measured using the immunofluorescence assays test (IFAT) .

Results

120 type1diabetic patients with clinical sign and symptom of insulin dependent diabetes mellitus, they are already diagnosed as having type1diabete mellitus, 91 patients of them shows positive serological titer of different pattern of auto-antibodies (Table1). Those with T1DM; 62 child of them appeared to have a positive antibodies (Ab's) titer for diabetes,13child shows positive Ab's titer for diabetes & Celiac disease , other 9 childs found to have positive Ab's titer related to diabetes & thyroiditis , the remaining seven,one of them have a positive Ab's against the thyroid gland, and the last five proved to be positive for Ab's concerned with CD and only one case appeared to have a positive titer antibodies for DMT1, CD ,and Thyroiditis (polyglandular auto-immune syndrome) (Table2).

while there are 57 child with a mean age of 11.1 year above nine year of age (tabl .3).

Table 5, 6,7,8, and 9 shows the important association of Thyroiditis and CD with T1DM in general.

Table (1).The prevalence of (+ve) and (-ve) auto-Abs.

TOTAL NUMBER OF PATIENTS	120
POSITIVE AUTO-ANTIBODY TITER	91
NEGATIVE AUTO-ANTIBODY TITER	29

Table (2).The prevalence of positive auto-Abs in autoimmune disorders.

(+Ve)Auto-Abs Titer For DM	(+Ve) Auto-Abs Titer For DM ,CD	(+Ve)Auto-Abs Titer For DM, Thyroiditis	(+Ve) Auto-Abs Titer For CD	(+Ve)Auto-Abs Titer For Thyroiditis	PAS
62	13	9	5	1	1

Table (3) Age distribution among autoimmune T1DM.

DISORDERS	BELOW TEN YEAR OF AGE GROUP	TEN YEAR AND ABOVE OF AGE GROUP
DMT1	20	42
DMT1 & CD	4	9
DMT1 & THROIDITIS	3	6
DMT1& CD & THROIDITIS	1	0
TOTAL NO.	28	57

Table (4). Sex distribution among autoimmune T1DM.

DISEASES	FEMAL	MALE
DM	29	33
DM + CD	3	10
DM + Thyroiditis	6	3
DM+CD+Thyroiditis	0	1
TOTAL NUMBER	47	38

Table (5). Prevalence of celiac disease in auto-immune type 1 diabetic children.

Age	Sex	Anti-insulin	Anti-IA2	Anti-GAD	Anti-Pancr	Anti-gliadin.A	Anti-gliadin.G	Anti-t TG.A	Anti-t TG .G
6	F	214.8		562.7		49.1	104.7		
10	M		264.6	581.7					19.8
8	M		133.5	114.1		71.8			
7	M	17.6	548			27	41		
7	F		89			305.6	20.8		
13	M	26.9					144.4		
15	M	17.9	28	62.17			38.7		
14	M	14.1					99.3		
15	M			17				19.7	
10	M			18.4		113.4	71.8	400.3	
14	M		427.1			39.6	49.6		
15	M			432.4		68.5			
12	F		310				80.6		

Table (6) .Positive auto-immune Abs (celiac diseases).

Age	Sex	Anti-GLA	Anti-GLG	Anti-t TGA	Anti-t TGG
5	M	104.4		25.4	57.3
10	F		109.4		
14	F			26.5	26
7	M	56.2			
15	F	41.7	115.5	916.9	109

Table(7).Prevalence of a positive thyroids auto-Abs with T1 DM

Age	Sex	Anti-insul.	Anti-IA2	Anti-GAD	Anti-Panc.	Anti-TG	Anti-TPO	TSH	T4	T3
12	M	67.1	255.7	272.6		300		0.7	98	2.4
10	M	41.6	245.5	32.6			800	1.5	86	1.4
5	F	52.9	54.6	21.9		122.5		2.6	110	2.3
9	F	32	228.9	357.3		3088	1662	10.2	67	2.1
15	F	16				132.5		1	86	2
7	M	10.8		355.8		213	55.5	4.8	118	2.8
13	F	18.8		228.6		302.7	63.4	2.3	86	1.6
10	F			96.5			56	1.9	85	2.1
11	M	66				116		8.59	55	1.66

Table (8). Auto-immune Thyroiditis

AGE	SEX	T3	T4	TSH	ANTI-TG	ANTI-TPO
7 YEAR	FEMAL	1.6	40	13.4	332	54

Table (9).Typical Polyglandular autoimmune syndrome (T1 DM , CD , Thyroiditis)

Age	Sex	T3	T4	TSH	Anti-insulin	Anti-IA2	Anti-GAD	Anti-Panc.	Anti-GLA	Anti-GLG	Anti-t TG	Anti-tTG	Anti-TG	Anti-TPO
8	M	2	45	12	24.5	10.8	29.3	0	0	0	250	0	267	153

Discussion

Interviews of participants revealed a wide range of associated autoimmune diseases as it is appeared in table (1,2). Celiac disease coexists with type 1 diabetes less frequently than does thyroiditis, Its prevalence in children and adolescents with type 1 diabetes ranges from 3 to 8% a much higher prevalence than that found in the general population(24). Thus routine screening of type 1 diabetes patients for celiac disease is recommended (22-24). Type 1 diabetes, a common autoimmune endocrine disease in children and adolescents, is frequently associated with other autoimmune diseases and autoantibodies (25). The most prevalent autoimmune disorders associated with type 1 diabetes is thyroiditis, Its prevalence varies from 8 to 50% depending on the age, sex, and ethnic origin of the subjects (30) and to compare with our study it was found that there were only 9.16% thyroiditis(11 patient), while celiac disease seems to be the most prevalent autoimmune disorder occupying 15.83%(19 patient) from overall of T1DM (120 patient). Moreover the percent of CD, Thyroiditis from autoimmune T1DM (85 child) will be 16.47%, 11.76% which is meaning that CD took more attention to look for than Thyroiditis in this study although both of them play associated to some

extent with T1DM.

Autoimmune T1DM seems to be more common in adolescents above nine year of age(67.05 %) than those children below ten year of age (32.94%), while there are no sex difference to attract attention in this study (Tabl 3,4).

Unfortunately intestinal biopsy as a diagnostic way for CD can't be accessible due to many difficulty facing the study yet clinical signs and symptoms in addition to the positive Abs titer can give us a clue and orientate our mind to that disorder. Although the pictures of our study doesn't goes fit with others yet the important subject in this study is to follow those children and adolescents of T1DM by the above investigations and to look for these problems as far as they are treatable and preventable too. This condition is inherited in an autosomal recessive pattern (27), and although there is some genetic role to play in the precipitation of this syndrome, yet we can do many thing for their prevention (gluten free diet, treatment with replacement therapy-- insulin for diabetes, thyroid hormone for thyroiditis, vitamin D and calcium for hypoparathyroidism, cortisol and fludrocortisones for Addison's disease rather than immunosuppressive drug which are not widely used with APS

but have been attempted with mixed results in a number of cases). Autoimmune polyglandular syndrome, type 1 which we studied her mostly is an inherited condition that affects many of the body's organs. although most of the characteristic features of autoimmune polyglandular syndrome, type 1 result from mutations in the *AIRE* gene which provides instructions for making a protein called the autoimmune regulator. More than 60 mutations in the *AIRE* gene have been identified in people with autoimmune polyglandular syndrome, type 1. Some of these genetic changes lead to the production of an abnormally short, nonfunctional version of the autoimmune regulator protein. Other mutations change single protein building blocks (amino acids) in critical regions of the protein. *AIRE* mutations reduce or eliminate the function of the autoimmune regulator protein. Without enough of this protein, the immune system can malfunction, resulting in autoimmunity(26).

For reasons that are unclear, defects in the autoimmune regulator protein primarily affect hormone-producing (endocrine) glands . In most cases, the signs and symptoms of autoimmune polyglandular syndrome, type 1 begin in childhood or adolescence and precipitated later , this could explain the large numbers of the affected patients above ten years of age appeared in this study . In the syndrome of APS, the chances are good that within a community of type 1 diabetics, there will be at least one or more autoimmune disorders exhibited here. APS is characterized by the development of at least two of the following: type 1 diabetes, Addison's disease, and autoimmune thyroid disease as in Graves' disease or Hashimoto thyroiditis (23). our study concentrate upon looking for

thyroiditis, celiac disease in type 1 diabetes and we hope to complete further studies so that to include other glands as the adrenal e.g Addison , and also to encompass other autoimmune disorders e.g oopharitis and arthritis and lastly to look for any invading microorganisms which could be the causative or the precipitating agents.

Conculsion; There are an increased prevalence of autoimmune thyroiditis and celiac diseases with type one diabetes mellitus specifically in adolescents.

References

1. Slover RH, Eisenbarth GS: Prevention of type I diabetes and recurrent B-cell destruction of transplanted Islets. *Endocr Rev* 18:241–258, 1997.
2. Anderson, M.S. (2008). Update in endocrine autoimmunity. *J. Clin. Endocrinol. Metab.* 93, 3663–3670.
3. Long, S.A., Cerosaletti, K., Bollyky, P.L., Tatum, M., Shilling, H., Zhang, S., Zhang, Z.Y., Pihoker, C., Sanda, S. Greenbaum, C., and Buckner, J.H. (2010). Defects in IL-2R signaling contribute to diminished maintenance of FOXP3 expression in CD4(+)CD25(+) regulatory T-cells of type 1 diabetic subjects. *Diabetes* 59, 407-415
4. Burek CL, Rose NR, Guire KE, Hoffman WH: Thyroid autoantibodies in black and white children and adolescents with type1 diabetes mellitus and their first degree relatives. *Autoimmunity* 7:157–167, 1990
5. R, ori5. Lni d'Annunzio G, Vitali L, Scaramuzza A: IDDM and autoimmune thyroid disease in the pediatric age group. *J Pediatr Endocrinol Metab* 9 (Suppl. 1): 89–94, 1996
6. Maugendre D, Massart C, Karacatsanis C, Guilhem I, Poirier JY, Sonnet E, Allanic H: Increased prevalence of thyroid autoantibodies

- and subclinical thyroid failure in relatives of patients with overt endocrine disease-associated diabetes but not type 1 diabetes alone. *Diabetes Metab* 23:302–307, 1997
7. Lindberg B, Ericsson UB, Ljung R, Ivarsson SA: High prevalence of thyroid autoantibodies at diagnosis of insulin-dependent diabetes mellitus in Swedish children. *J Lab Clin Med* 130:585–589, 2000
 8. Chang CC, Huang CN, Chuang LM: Autoantibodies to thyroid peroxidase in patients with type 1 diabetes in Taiwan. *Eur J Endocrinol* 139:44–48, 1998
 9. McCanlies E, O'Leary LA, Foley TP, Kramer MK, Burke JP, Libman, Swan JS, Steenkiste AR, McCarthy BJ, Trucco M, Dorman JS: Hashimoto thyroiditis and insulin-dependent diabetes mellitus: differences among individuals with and without abnormal thyroid function. *J Clin Endocrinol Metab* 83:1548–1551, 1998
 10. Roldan MB, Alonso M, Barrio R: Thyroid autoimmunity in children and adolescents with type 1 diabetes mellitus. *Diabetes Nutr Metab* 12:27–31, 1999
 11. Verge CF, Howard NJ, Rowley MJ, Mackay IR, Zimmet PZ, Egan M, Hulinska H, Hulinsky I, Silvestrini RA, Kamath S, et al: Anti-glutamate decarboxylase and other antibodies at the onset of childhood IDDM: a population based study. *Diabetologia* 37:1113–1120, 1994
 12. Calero P, Ribes-Koninckx C, Albiach V, 12. Calero P, Ribes-Koninckx C, Albiach V, Carles C, Ferrer J: IgA antigliadin antibodies as a screening method for nonovert celiac disease in children with insulin dependent diabetes mellitus. *J Pediatr Gastroenterol Nutr* 23:29–33, 1996
 13. Acerini CL, Ahmed ML, Ross KM, Sullivan PB, Bird G, Dunger DB: Coeliac disease in children and adolescents with IDDM: clinical characteristics and response to gluten-free diet. *Diabet Med* 15: 38–44, 1998
 14. Vitoria JC, Castano L, Rica I, Bilbao JR, Arrieta A, Garcia-Masdevall MD: Association of insulin-dependent diabetes mellitus and celiac disease: a study based on serologic markers. *J Pediatr Gastroenterol Nutr* 27:47–52, 1998.
 15. Fraser-Reynolds KA, Butzner JD, Stephure DK, Trussell RA, Scott RB: Use of immunoglobulin A-antiendomysial antibody to screen for celiac disease in North American children with type 1 diabetes. *Diabetes Care* 21:1985–1989, 1998
 16. Carlsson AK, Axelsson IEM, Borulf SK, Bredberg ACA, Lindberg BA, Sjoberg KG, Ivarsson S-A: Prevalence of IgA-antiendomysium and IgA-antigliadin autoantibodies at diagnosis of insulin-dependent diabetes mellitus in Swedish children and adolescents. *Pediatrics* 103:1248–1252, 2001
 17. Parnell N, Ciclitira PJ: Celiac disease. *Curr Opin Gastroenterol* 15:120–124, 1999
 18. Tomer, MD, FACP, FACE, Yaron. "Genetic Susceptibility to Autoimmune Endocrine Disorders." *InFocus Newsletter* Vol. 12, No. 3. Sept. 2004. American Autoimmune Related Diseases Association. 10 Apr 2007.
 19. Majeroni, MD, Barbara, and Patel, MBBS, Parag, "Autoimmune Polyglandular Syndrome, Type 2."
 20. American Family Physician. 1 Mar. 2007. American Academy of Family Physicians. 10 Apr 2007.
 21. Abbas Ali Mansour MD1. The association of diabetes and hyperthyroidism in Basra. *The new Iraqi Journal of Medicine* 2011;7:30–34.
 22. Kahaly GJ. Polyglandular autoimmune syndromes. *Eur J Endocrinol*. Jul 2009;161(1):11–20. Epub 2009 May 1.
 23. Husebye E.S., Anderson M.S.

(2010). Autoimmune Polyendocrine Syndromes: Clues to Type 1 Diabetes Pathogenesis. *Immunity*, 32 (4), pp. 479-487. 2 Iacovelli P, Sinagra JL, Vidolin AP, Marenda S, Capitanio B, Leone G, Picardo. Relevance of thyroiditis and of other autoimmune diseases in children with vitiligo. *Dermatology* 2005;210:26-30.

25. Oki K, Yamane K, Koide J, Mandai K, Nakanishi S, Fujikawa R, Kohno N. A case of polyglandular autoimmune syndrome type III

complicated with autoimmune hepatitis. *Endocr J*. 2006 Oct;53(5):705-9. Epub 2006 Sep 1.

26. Schumann C, Faust M, Gerharz M, Ortmann M, Schubert M, Krone W. Autoimmune polyglandular syndrome associated with idiopathic giant cell myocarditis. *Exp Clin Endocrinol Diabet* es. 2005 May;113(5):302-7.

27. Caturegli P, Kimura H, Rocchi R, Rose NR. Autoimmune thyroid diseases. *Curr Opin Rheumatol*. 2007; 19: 44-48.