Academic Sciences International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 6 Issue 2, 2014

Research Article

COEXISTENCE OF AUTOIMMUNE DISEASE WITH TYPE I DIABETES MELLITUS IN LIBYAN PATIENTS

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Received: 17 Dec 2013, Revised and Accepted: 11 Feb 2014

ABSTRACT

Objective: Type I diabetes mellitus (TIDM) is usually associated with autoimmune thyroid disease (AITD), celiac disease (CD) and Addison's disease (AD). The aim of this study was to determine the prevalence of AITD, CD and AD among Libyan patients with type I diabetes mellitus.

Methods: The prospective clinical study was undertaken on 849 patients (554 females and 295 males) admitted in endocrine department of Tripoli Medical Center from December 2007 to July 2008. Patients serum level of thyroxin (T_4), triiodothyronin (T_3), free thyroxin (FT_4), free triiodothyronin (FT_3), thyroid stimulating hormone (TSH) and thyroid peroxidase antibody (TPOAb) and thyroglobulin antibody (TGAb) were measured for 748 patients while 101 patients of type I diabetes mellitus patients were included in this study investigated for celiac disease and Addison disease by measuring tissue transglutaminase antibody (TTGAb) and endomysial antibody (EMAAb) in celiac disease, and 21-hydroxylase antibody (21-OHAb) in Addison's disease. The venous blood samples were taken from all the subjects in the morning after fasting overnight.

Results: From 748 TIDM patients screened for AITD, 28.74% of cases have thyroid dysfunction, 21.26% have hypothyroidism (66% of females and 34% of males), and 7.49% have hyperthyroidism (75% of females and 25% of males). From 101 TIDM patients screened for CD and AD, 4.95% of cases have CD (80% of females and 20% of males) and we did not come cross any case of AD.

Conclusion: From the previous results we conclude that the prevalence of AITD, CD and AD in children with TIDM is high especially among female patients.

Keywords: Addison's Disease, Autoimmune Thyroid Disease, celiac disease, Type 1 diabetes mellitus.

INTRODUCTION

Autoimmune disease is a clinical syndrome caused by the activation of T cells, B cells, or both, in the absence of an ongoing infection or other discernible cause [1], in this disease the tissue damage is caused by an adaptive immune response to self-antigen [2], and they are classified in to Organ specific and Non-organ specific. There are many Factors that influence the development and expression of autoimmune diseases; these factors include Genetic predispositions, Environmental, the effect of sex hormones and stress [2-4]. Several mechanisms are thought to be operative in the pathogenesis of autoimmune diseases; these mechanisms include T-Cell bypass, Molecular Mimicry, Cytokine Dysregulation and Dendritic cell apoptosis [5]. Diabetes mellitus is metabolic disorder of multiple etiologies characterized by chronic hyperglycemia with disturbance of Carbohydrate, fat and protein metabolism resulted from defects in insulin secretion, insulin action, or both. Insulin is produced by beta cells of the islet of Langerhans located in the pancreas [6]. Diabetes Mellitus Classified into Type I diabetes mellitus [insulin-dependent diabetes mellitus (IDDM)] and Type II diabetes mellitus [non–insulin-dependent diabetes mellitus (NIDDM)]. Type I diabetes mellitus is an autoimmune disease that results in the permanent destruction of insulin-producing beta cells of the pancreas. As a result, the insulin is functionally absent [6]. IDDM occurs most commonly in juveniles but can occur in adults, especially in those in their late 30s and early 40s [7].

Autoimmune diseases usually occur together in defined syndromes with distinct pathophysiology and characteristics; type I diabetes mellitus (TIDM) is usually associated with autoimmune thyroid disease (AITD), celiac disease (CD) and Addison's disease (AD). The reason for this is the genetic risk while the genetic risk for these diseases overlaps and includes genes within the major histocompatibility complex (MHC) such as the human leukocyte antigens (HLA) DR and DQ alleles. The major histocompatibility complex (MHC) has been extensively studied in these diseases. The highest-risk human leukocyte antigen (HLA) genotype for TIDM is DR3-DQ2, DR4-DQ8. Subjects expressing this genotype have a 5% risk for TIDM by 15 years of age. Screening blood donors for thyroid peroxidase (TPO) autoantibodies has shown an association with DR3 and DR5. Other studies have failed to confirm this association [5]. In families with multiple members affected with TIDM and AITD, DR3-DQ2 has been linked with AITD and TIDM. Cross-sectional analysis in subjects with TIDM has shown an association with the genotype DR3-DQ2, DR4-DQ8. DR3-DQ2 shows a strong association with CD. Homozygosity for DR3-DQ2 in a population with IDDM carries a 33% risk for the presence of tissue transglutaminase (TTG) autoantibodies. Three percent of children from the general population with one or two DR3-DQ2 alleles have CD defined by intestinal biopsy or are persistently positive for TTG autoantibodies by 5 years of age. AD has been associated with the presence of a rare subtype of DR3-DQ2, DR4-DQ8 in which the DR4 subtype is DRB1*0404. This subtype is found in less than 1% of the general population compared with 30% of the population with AD. Some HLA alleles are protective for disease development. DQA1*0102, DQB1*0602 is associated with a low risk for TIDM [5]. The present study was carried out to give background on autoimmune diseases (type I diabetes mellitus, autoimmune thyroid disease, celiac disease and Addison's disease), to study the factors that lead to occurrence of these autoimmune diseases (autoimmune thyroid disease, celiac disease and Addison's disease) in type I diabetes mellitus patients, to study the effect of these autoimmune diseases on diabetes control and to determine the prevalence of these autoimmune diseases among Libyan patients with diabetes.

MATERIAL AND METHODS

The prospective clinical study was undertaken on 849 patients admitted in endocrine department of Tripoli Medical Center from December 2007 to July 2008. From the patients files, the concomitant disease presence or absence was also recorded; especially with reference thyroid function. The important investigations as prescribed by the physician were also recorded. patient's serum level of T_4, T_3, FT_4, FT_3 and TSH were

measured for 748 patients. The venous blood samples were taken from all the subjects in the morning after fasting overnight while TPOAb and TGAb level were measured abroad. 101 of patients with type I diabetes mellitus were included in this study were investigated for celiac disease and Addison disease. Both diseases were diagnosed abroad. Celiac disease patients have been diagnosed by finding a positive anti-tissue transglutaminase (TTG) test and Addison disease diagnosed by finding positive 21-OH antibody. The present study was approved and done according to ethics guidelines of Tripoli Medical Center.

Specimen collection and preparation for analysis

Blood samples were collected into polyethylene test tubes. SST tubes were used for serum collection. From BD Vacutainer CO., Belliver Industrial Estate, Plymouth. Serum was separated by centrifuge for 5 min at 3,000 rpm to eliminate cell debris using Heraeus centrifuge from Germany. Serum samples were stored at -20°C until assay.T_4; T_3, FT_4, FT_3 and TSH were measurement by the Multi-channel Analyzer (ELYCSES 2010) from Roche, Germany.

RESULTS

There were 849 patients (554 females and 295 males) with type I diabetes mellitus included in this study, with clinical evidence of classical manifestations of diabetes mellitus and confirmed biochemically by finding abnormally high blood glucose level more than one occasions.

Examination of these figures reveal that the incidence of autoimmune thyroid diseases was significantly ($P < 0.05$) increased in type I diabetes mellitus subjects studied compared with normal population. In table 1 and figure 1 demonstrate the prevalence of autoimmune thyroid diseases in 748 patients with diabetes mellitus.

In this study we found a total of 215 patients (28.74%) have thyroid dysfunction. In which 159 patients (21.26%) diagnosed as hypothyroidism and 56 patients (7.49%) have hyperthyroidism.

Examination of figure 2 demonstrates that the number of patients with type I diabetes mellitus have hypothyroidism are 159 patients (21.26%), 105 females and 45 males,

This results show that about 66% of the hypothyroidism patients belonged to female sex whereas only 34% of these cases were belong to male sex.

This female predominance in the present study is also documented in different reports. Examination of figure 3 demonstrates that the number of patients with type I diabetes mellitus have hyperthyroidism are 56 patients (7.49%), 42 females (75%) and 14 males (25%). Also the hyperthyroidism show female predominance.

Table 1: The prevalence of autoimmune thyroid disease in patients with type I diabetes mellitus.

	Total			Euthyiroidism			Hypothyroidism			Hyperthyroidism		
	T	F	M	T	F	M	T	F	M	T	F	M
No	748	487	261	533	340	193	159	105	54	56	42	14
%		65.1	34.9	71.3	63.8	36.2	21.3	66	34	7.5	75	25

T: Total, F: Female, M: Male, No: Number and %: Percentage

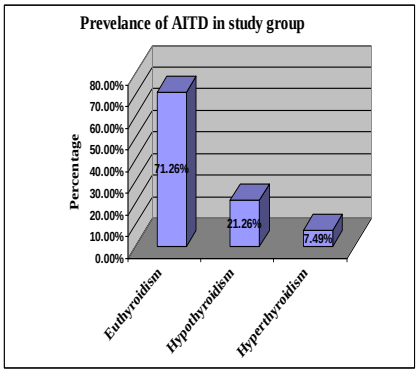

Fig. 1: Prevalence of autoimmune thyroid disease (AITD) in the study group.

There were 101 patients with type I diabetes mellitus (67 females and 34 males) examined for celiac disease and Addison's disease.

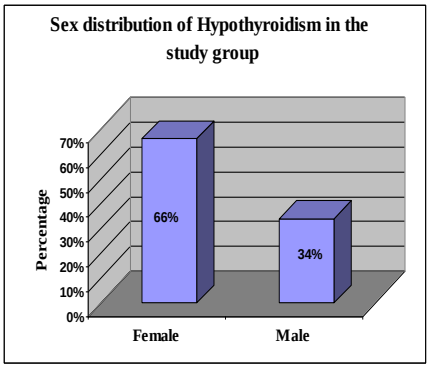

Fig. 2: Sex distribution of autoimmune hypothyroidism in the study groups.

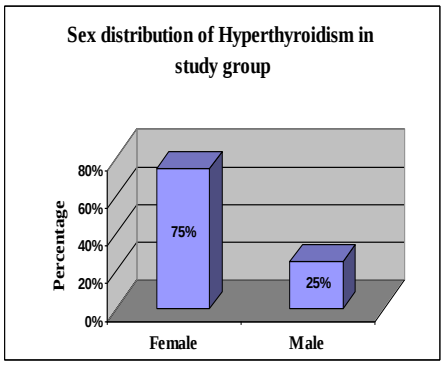

Fig. 3: Sex distribution of autoimmune hyperthyroidism in the study groups.

In table 2 and figure 4 reveal that patients with diabetes had a significantly higher incidence of Celiac disease. 4.95% of patients with type I diabetes mellitus studied were confirmed with the TTG as having celiac disease, and we did not come cross any case of Addison disease. Examination of figure 5 demonstrates that the number of patients with type I diabetes mellitus have celiac disease are 5 patients (4.95%), 4 females (80%) and 1 male (20%).also the celiac disease show female predominance.

Table 2: The prevalence of Celiac disease and Addison's disease in patients with type I diabetes mellitus.

	TOTAL			CD			AD		
	T	F	M	T	F	M	T	F	M
No	101	67	34	5	4	1	0	0	0
%		66.34	33.66	4.95	80	20	0	0	0

T: Total, F: Female, M: Male, No: Number and %: Percentage.

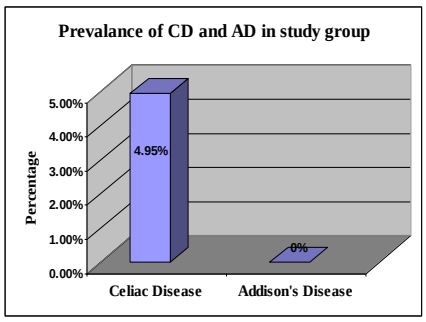

Fig. 4: The prevalence of Celiac Disease and Addison's Disease in the study group.

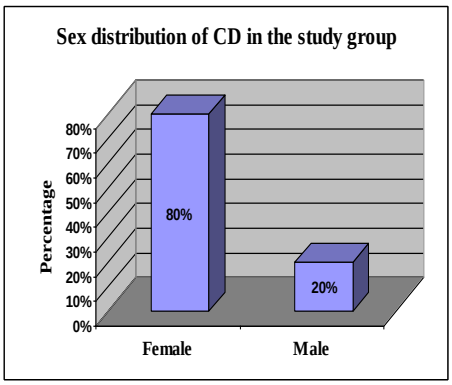

Fig. 5: Sex distribution of Celiac Disease in the study groups.

The present study shows that the age range is 1-25 years with the highest prevalence was between 10-15 years.

DISCUSSION

The aim of this study was to determine the prevalence of autoimmune diseases among Libyan patients with type I diabetes mellitus. The prevalence of these autoimmune diseases among patients with type I diabetes mellitus is conflicting at present. Very few studies have dealt with the relationship of autoimmune diseases and type I diabetes mellitus and there is only one study is available from Libya as far as we know. Autoimmune diseases arise from an overactive immune response of the body against substances and tissues normally present in the body. In other words, the body attacks its own cells. Autoimmune diseases are a major cause of immune-mediated diseases.

The causes of autoimmune diseases are still obscure, most autoimmune diseases are probably the result of multiple circumstances, for example, a genetic predisposition triggered by an infection. Sex seems to have a major role in the development of autoimmunity; most of the known autoimmune diseases tend to show a female preponderance, the reasons for this are unclear. Apart from inherent genetic susceptibility, several animal models suggest a role for sex steroids. Another theory suggests that the female have higher tendency to get autoimmunity is due to an X chromosome.

Type I diabetes mellitus (TIDM) is characterized by autoimmune destruction of beta cells precipitated by environmental insults in genetically susceptible individuals. In this study, we were focusing on two factors, genetic predisposition and autoimmunity, in its pathogenesis and in the causation of its various associations. This may throw some light on the link between these conditions. The major histocompatibility complex (MHC) has been extensively studied in type I diabetes mellitus. The human leukocyte antigen (HLA) genotype with the highest risk for TIDM is DR3-DQ2 and DR4-DQ8. Subjects expressing this genotype have a 5% risk for developing TIDM by the age of 15 years. Studies have shown the co-occurrence of autoimmune and genetic disorders in association with TIDM. The existence of disease-specific auto-antibodies and predisposing HLA types in patients of TIDM makes them more prone to develop these associated autoimmune conditions. Knowledge about these associations and regular screening for them can help in their early diagnosis and management [8].

TIDM is associated with autoimmune thyroid disease (AITD), celiac disease (CD), Addison's disease (AD), and other autoimmune diseases. These diseases can occur together in defined syndromes with distinct pathophysiology and characteristics: autoimmune polyendocrine syndrome I, and II [5].

APS-I also known as autoimmune polyendocrinopathy candidiasis ectodermal dysplasia (APECED) is a rare polyendocrine autoimmune disease caused by mutations of the autoimmune regulator gene (AIRE). APS-I is defined by the presence of two or three of the following components: mucocutaneous candidiasis, adrenal insufficiency, and hypoparathyroidism. Affected individuals generally develop persistent or recurrent mucocutaneous candidiasis within the first several years of life. Autoimmune hypoparathyroidism is usually the first autoimmune disorder to present, followed by AD, additional autoimmune disease developing sequentially over time. Approximately 20 % of subjects with APS-I have TIDM. APS-II is defined as the association of an autoimmune endocrine disorder with an additional autoimmune disease but not meeting the criteria for APS-I or having an identified mutation of the AIRE gene. The majority of patients with TIDM who have another autoimmune disease are diagnosed with that disease after the onset of diabetes [5]. These diseases are autoimmune-mediated adrenal insufficiency and autoimmune-mediated thyroiditis [9]. CD also may be diagnosed at onset of diabetes; however, significant subsets of subjects with diabetes who develop CD-related autoimmunity do so after diabetes onset [5].

Graves disease is the most common form of hyperthyroidism, and is caused by anti-thyroid antibodies that have the effect of stimulating the thyroid into overproduction of thyroid hormone, and Hashimoto`s disease is a common form of hypothyroidism, characterised by initial inflammation of the thyroid, and, later, dysfunction and goiter. There are several characteristic antibodies (e.g., anti-thyroglobulin).

Thyroid autoimmunity was more common in females particularly after the age of 12 years and increased with longer duration of diabetes [10]. Patients who developed thyroid dysfunction were older at type I diabetes diagnosis than those who did not, patient with TPO-Ab positive were 17.9 times more likely to develop thyroid dysfunction [11].

AITD forms a major subset of autoimmune endocrine disorders associated with TIDM. As much as 20-30 % of the population with TIDM expresses thyroid peroxidase (TPO) and/or thyroglobulin (TG) autoantibodies, whereas they are expressed in only 13 and 11% of the general population, respectively. Long-term follow-up suggests that as much as 30% of patients with TIDM develop AITD. Hypothyroidism is present more commonly in subjects with TIDM than Hyperthyroidism, similar to that in the general population [8].

Prospective studies were undertaken on 849 Libyan patients with type I diabetes mellitus of either sex were regular attendance at the outpatient clinic in the Pediatric Endocrine Department at Tripoli Medical Center. Apart from routine investigations serum thyroid function tests were estimated for 748 cases at the time of admission or during routine checkup.

In the present investigation we encountered 215 patients (28.74%) have thyroid dysfunction. 159 patients (21.26%) have hypothyroidism and 56 patients (7.49%) have hyperthyroidism.

This results shows that patients with diabetes had a significantly higher incidence of hypothyroidism (21.26%) which were more than two folds those of the normal people and only 7.49 % are hyperthyroidism.

This is in agreement with Aaron Hanukoglu et al whose found in their study that the prevalence of autoimmune thyroiditis was 27 and 25% for probands and relatives, respectively. Also our results were in agreement with Barker whose found that the incidence of patients with autoimmune thyroid disease was 15 to 30% of subjects with TIMD.

Umpierrez et al [12] prospectively followed 58 patients type I diabetes for 18 years by monitoring TSH, T3, and T4 every year, thyroid peroxidase Abs every 4 years, He found 33% of the patients have thyroid dysfunction (18 patient's hypothyroidism and 1 patient hyperthyroidism). Hypothyroidism was more common in female than in male subjects and in patients with positive TPO antibodies.

Several reported inconsistent results in contrast with what has been found in this study. Jayaraman et al [8], in a study included 214 patients with type I diabetes observed only 6% of the studied patients have hypothyroidism 1% of cases were hyperthyroidism.

Hyperthyroidism is much less commonly reported, with a prevalence of 1%, similar to that in the general population. In addition Malcová et al [13] found in a study included 868 patients with type I diabetes mellitus, age younger than 18 years, thyroid disease was significantly more in patients with type I diabetes mellitus (10.0% vs. 1.9%) and their siblings (3.1% vs. 1.7%). Pimenta et al [14] unexpectedly in a study of 256 patient with type I diabetes mellitus, thyroid disease was found significantly more in type I diabetes mellitus (10.0% vs. 1.9%) and their siblings (3.1% vs. 1.7%). Celiac disease occur when portion of the small intestine exposure to certain dietary gluten proteins.

In our study we found 5 patients (4.95%) of the studied group have celiac disease. These patients have been diagnosed abroad by finding a positive anti-tissue transglutaminase (TTG) test. The prevalence of celiac disease in patients with TIDM is approximately 20 times higher than in the general population [15]. Patients without celiac disease were significantly younger at diabetes onset [16]. In agreement with our study Barker [5] observed 4–9% of patients with type I diabetes mellitus have celiac disease. Elsewhere, the prevalence of celiac disease among probands and screened relatives was 8.3 and 6%, respectively. These rates were higher than those for control subjects and the 312 family members interviewed only (0.1 and 0.3%, respectively) [17]. Approximately 5-10% of subjects with type I DM are positive for endomysial antibody (EMA) or transglutaminase (TTG) autoantibodies and a significant proportion (up to 75%) have abnormalities on biopsy of the intestine [8]. Prevalence of celiac disease was also higher in patients with type I diabetes mellitus than in controls (3.2 % vs. 0.5 %), but it does not differ in their first-degree relatives [13].

Ashabani et al [18] investigated 234 Libyan children with DM (121 males and 113 females) age between 2 and 25 years and 50 healthy school children for CD by measuring IgA and IgG antigliadin (AGA), anti-tissue transglutaminase, and anticalreticulin antibodies, in this study they found 21.3% were positive for IgA- and/or IgG-AGA, TTG, and anticalreticulin antibodies. 19 of these patients were EmA positive and 7 were EmA negative. The prevalence of CD in this study was thus 10.3%. The prevalence of CD in patients with type I diabetes mellitus in Libya was found to be higher than in several European countries. Addison Disease is often caused by autoimmune destruction of the adrenal cortex. Addison Disease is infrequently associated with TIDM. Adrenal antibodies (antibody to 21-hydroxylase) are seen in approximately 1.5% of cases of TIDM, of whom 15% develop Addison's disease (AD) during follow up [8]. Overall prevalence of AD in type I DM higher than general population but in our study we did not come cross any case of Addison disease. In a recent study by Kerner et al [19] found that six individuals were diagnosed with AD (0.2%); five were identified on initial endocrine evaluation, and in other study by Barker found 0.5% of IDDM patients have Addison's disease. Autoimmune adrenal disease is infrequently associated with TIDM. Jayaraman et. al [8] observed that Adrenal antibodies (antibody to 21-hydroxylase) are seen in approximately 1.5% of cases of TIDM, of whom 15% develop AD during follow-up. Overall prevalence of AD in type I DM has been reported to be 0.5%. Adrenal and thyroid autoimmunity coexist approximately 70% of the time.

CONCLUSION

This study provides definitive evidence of the association between autoimmune disease (AITD, CD, and AD) and type I diabetes mellitus which are associated with the production of organ-specific autoantibodies. The incidence of these diseases was higher in women, especially those with positive antibodies. The high prevalence of these diseases may be explained by shared genetic susceptibility, the genetic risk for these diseases overlaps and includes genes within the major histocompatibility complex (MHC) such as the human leukocyte antigens (HLA) DR and DQ alleles and the MHC I-related gene A (MIC-A). For these reasons the frequent screening and the follow-up of patients with type I diabetes especially those with positive autoantibodies are necessary.

RECOMMENDATION

This study confirms the association between autoimmune disease (autoimmune thyroid disease, celiac disease, Addison disease) and type I diabetes, so we suggest that all subjects with type I diabetes should undergo screening of autoantibodies due to increased risk of these autoimmune disease among those patients. The patients with type I diabetes mellitus should undergo annual screening by measuring serum TSH and TPO antibodies to detect asymptomatic thyroid dysfunction, and due to increased risk of celiac disease among patients with diabetes they required a long follow-up by measure autoantibody (TTG, EMA)

every 2 years, and due to increased risk of Addison disease among patients with type I diabetes mellitus, these patients should undergo screening of 21-OH antibody every 2 years [5].

CONFLICT OF INTEREST

The authors have no conflicts of interest.

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