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Thyroid dysfunction and thyroid autoimmunity in Saudi type 2 diabetics

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Abstract Diabetes mellitus and thyroid disease are common endocrine disorders in the general population. To investigate the association between thyroid dysfunction, thyroid autoimmunity and Saudi type 2 diabetics, a random sample of 100 Saudi type 2 diabetics and 100 age- and sex-matched controls were studied. The mean age was 54 years for diabetics and 55 years for controls while the male:female ratios were 1:1.6 and 1:14 respectively. GAD65ab were found in 26% diabetics and 2% controls ($p=0.001$). Thyroid autoimmunity were detected in 10% diabetics vs. 5% controls ($p=0.05$), while thyroid dysfunction was found in 16% and 7% respectively ($p=0.03$). In GAD65ab-positive diabetics, thyroid autoimmunity was

observed in 27% vs. 4% GAD65ab-negative diabetics ($p=0.02$) and thyroid dysfunction was reported in 42% and 7% respectively. We conclude that thyroid dysfunction and autoimmunity are common in Saudi type 2 diabetics. Further studies are needed on the cost effectiveness of thyroid screening in diabetics.

Key words Thyroid dysfunction • Type 2 diabetes • GAD65ab • Thyroid autoimmunity • Saudi

Introduction

Diabetes mellitus (DM) and thyroid disease are common endocrine disorders in the general population. Worldwide the prevalence of diabetes for all age groups was estimated to be 2.8% in 2000 and is supposed to reach 4.4% in 2030. The total number of people with DM is projected to rise from 171 million in 2000 to 360 million in 2030 [1]. The prevalence of DM is highly variable between different populations. In Saudi Arabia the prevalence has doubled over the last two decades from 5% to 12% [2, 3] and reports suggest that it is present in epidemic proportions throughout the country [4]. Thyroid disease is also common in the general population. The Whickham survey found that thyroid dysfunction affected 6.6% of adults [5].

There is a recognised association between diabetes and thyroid disease, which has long been reported. In 1979 Feely and others studied the relation between DM and thyroid dysfunction [6, 7] and since then there have been many reports on the prevalence of thyroid dysfunction in diabetics. Smithson [8] reported a prevalence of undiagnosed thyroid disease in 5.5% of diabetics receiving community diabetes care while the prevalence in the entire population of diabetic patients registered in general practice was 10.8%. Perros et al. [9] studied a randomly selected group of 1310 diabetic adults and the overall esti-

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mated prevalence of thyroid disease was found to be 13.4%. A higher prevalence of abnormal TSH concentration in type 2 diabetic patients (31%) was reported by Celani et al. [10].

Although several studies have shown the association between thyroid autoimmunity and type 1 diabetes [11–15], little is known of the risk of thyroid autoimmunity in subjects with type 2 diabetes with GAD65 antibodies (LADA) [16–18].

To the best of our knowledge, no studies have been done to evaluate thyroid dysfunction and autoimmunity in Saudi diabetics. As DM is common in Saudi Arabia, we aim in this work to investigate the association between thyroid dysfunction, thyroid autoimmunity and Saudi type 2 diabetics for possible recommendation for screening of thyroid disease in Saudi type 2 diabetics.

Research design and method

Subjects

The study was a case–control study, conducted at King Abdulaziz University Hospital (KAUH), a teaching hospital in the western region of Saudi Arabia. A random sample of 100 Saudi type 2 diabetics (defined as diabetics diagnosed after the age of 35 years who were oral hypoglycaemic for at least 6 months) and 100 age- and sex-matched controls were recruited for this study from the medical outpatient clinic over 6 months. Exclusion criteria included all patients with thyroid disease, history of neck irradiation, patients with chronic renal failure, severe illness (like infection, recent myocardial infarction, severe heart failure, recent intensive care admission) and those on drugs which can interfere with thyroid function like beta-blockers, amiodarone and interferon- α . All participants gave informed consent and the study was approved by the ethical committee.

Measurements

venous blood samples from the study group were analysed for the presence of anti-peroxidase antibodies (anti-TPO), anti-thyroglobulin antibodies (anti-TG), islet cell antibodies (ICA512) and glutamic acid decarboxylase antibodies (GAD65ab). Other laboratory investigations included HbA1c and thyroid function test (TSH, free T3, free T4). Samples were either directly analysed from venous blood samples or serum was frozen at -20°C until analysed. The thyroid function test in our hospital is done using the electrochemiluminescence method. The normal range for TSH is 0.27–4.2 mU/l, for free T4 12–22 pmol/l and for free T3 2.8–7.1 pmol/l. Islet cell antibodies (ICA512) and glutamic acid decarboxylase antibodies (GAD65ab) were analysed by ELISA kits (RSR Ltd, Cardiff, UK and Biomerica, Newport Beach, Canada). Serum anti-TPO were analysed by immunometric enzyme immunoassay for the quantitative determination of antibodies against thyroid peroxidase (ORGENTEC Diagnostika GmbH, Mainz, Germany).

Analytical method

The following data were also collected: age, sex, BMI (defined as weight/height squared) as well as duration of diabetes and presence of poor glycaemic control (defined as HbA1c > 8% on 2 consecutive occasions). Patients were diagnosed to have:

1. Overt hypothyroidism when TSH > 4.2 mU/l and free T4 < 12 pmol/l and/or free T3 < 2.8 pmol/l.
2. Overt hyperthyroidism when TSH < 0.27 mU/l and free T4 > 22 pmol/l and/or free T3 > 7 pmol.
3. Subclinical hypothyroidism when TSH > 4.2 mU/l with normal free T4 and free T3.
4. Subclinical hyperthyroidism when TSH < 0.27 mU/l with normal free T4 and free T3.
5. Latent autoimmune diabetes of adults (LADA) was defined as type 2 diabetics with positive GAD65ab.

Comparison between cases with diabetes and control was done regarding islet cell autoantibodies (ICA), thyroid autoantibodies and thyroid dysfunction. Comparison between LADA and type 2 diabetics was made regarding thyroid autoantibodies, thyroid dysfunction, duration of diabetes, degree of blood glucose control, age and BMI.

Statistical analysis

Statistical analysis was done using Statistical Package for Social Sciences (SPSS 9.2). Different types of statistical methods were used when appropriate. Mean \pm SD was determined for quantitative data and frequency for categorical variables. Independent t-test was performed in all continuous variables. Normal distribution of the data was checked before any t-test. Chi-square was used to analyse group difference for categorical variables. A *p* value < 0.05 was considered significant.

Results

The mean age of the diabetic group was 54 ± 11.8 years (male:female 39:61) and 55 ± 10 years (male:female 41:59) for the control group. The mean duration of diabetes was 8.3 ± 3.9 years. GAD65ab were found in 26% of diabetics vs. 2% in the control group ($p=0.001$). In diabetics GAD65ab tend to be more frequent in females compared to males (2.3:1). Thyroid autoimmunity and dysfunction were significantly higher in diabetics compared to controls (Table 1). LADA patients were younger, had lower BMI and short duration of diabetes compared to type 2 diabetics (Table 2). Thyroid autoimmunity, measured by anti-TPO and anti-TG, was significantly higher in LADA compared to type 2 diabetics; 7/26 (27%) and 3/74 (4%) respectively ($p=0.02$).

Subclinical hypothyroidism and hypothyroidism were the commonest thyroid dysfunction in all groups, LADA, type 2 diabetics and controls (Table 3). Thyroid autoimmunity was commonly detected in LADA patients

Table 1 Shows ICA, thyroid autoimmunity and dysfunction in diabetics and controls

Variable	Diabetics n=100 (%)	Controls n=100 (%)	p value
GAD65ab	(26)	(2)	0.006
ICA512	(4)	(2)	0.35
Anti-TPO	(10)	(5)	0.05
Anti-TG	(10)	(5)	0.05
Thyroid dysfunction	(16)	(7)	0.03

GAD65ab, glutamic acid decarboxylase antibodies; *ICA512*, islet cell antibodies; *anti-TPO*, thyroid peroxidase antibodies; *anti-TG*, thyroglobulin antibodies

Table 2 Comparison between LADA and type 2 diabetics according to some variables

Variables	LADA n=26	Type 2 diabetics n=74	p value
Age in years, mean±SD	49.8±10	55.3±8.4	0.04
Sex, male:female	1:2.3	1.2:1	0.02
BMI, mean±SD	27.1±2.1	29±1.4	0.001
Duration of DM in years, mean±SD	5.5±3.5	8.3±3.8	0.05
Poor blood glucose control, n (%)	13 (50)	36 (48)	0.9

BMI, body mass index; poor blood glucose, HbA_{1c}>8%; *LADA*, latent autoimmune diabetes of adults

Table 3 Thyroid dysfunction in different groups

Thyroid dysfunction	LADA n=26	Type 2 diabetes n=74	Control n=100
Subclinical hypothyroidism	6	3	4
Hypothyroidism	4	2	2
Subclinical hyperthyroidism	0	0	1
Hyperthyroidism	1	0	0
Total, n (%)	11 (42)	5 (7)	7 (7)

LADA, latent autoimmune diabetes of adults

with thyroid dysfunction; it was 5/11 (45%), while it was 1/5 (20%) in type 2 diabetics and 1/7 (14%) in the control group.

Discussion

DM is a major public health problem. There are two major types of DM: type 1 and type 2. The two forms have different genetic background, demographic and biochemical characteristics, pathogenic mechanisms and type of treatment. It is well known that the majority of those with type 1 DM have autoimmune bases for the pathogenesis of their DM, which is supported by the frequent presence of ICA and GAD antibodies. Several studies have shown the increasing prevalence of autoimmune thyroid disease in patients with type 1 DM ranging from 25 to 50% [11–15]. It is the common genetic background that is responsible for

the association of several endocrine autoimmune diseases in the so-called autoimmune polyendocrine syndromes. Thus, the polymorphism of both HLA class II DR-DQ genes and the CTLA-4 gene is associated with genetic risk for type 1 DM, thyroid and Addison's disease [19, 20].

For type 2 DM, it has been shown that many subjects who develop secondary failure to sulphonylurea treatment are positive for ICA, especially for GAD65ab [21, 22]. These types of patients are identified as LADA [23]. The absolute risk of slowly progressive adult-onset autoimmune diabetes is three to four fold that of childhood and adolescence type 1 DM [24].

There is increased prevalence of thyroid disease in type 2 diabetics, but it has a lower prevalence (19%) compared to in type 1 DM [16]. However, in LADA a higher prevalence reaching 24% has been reported [25, 26]. Our findings are in agreement with what has been reported. The increased risk for thyroid autoimmunity observed in GAD65ab-positive subjects supports the hypothesis that

LADA is one of the phenotypic expressions of the complex autoimmune polyendocrine syndrome. Gambelunghe et al. [25] reported that the presence of HLA-DR3-DQ2 is associated with increased risk of thyroid and adrenal autoimmunity in these patients.

Interestingly, our study showed a higher prevalence of LADA in Saudi type 2 diabetics (26%) compared to reports from other parts of the world, which showed a prevalence ranging from 2.5 to 16% [12, 24, 25, 27–29]. This could be related to difference in the histocompatibility (HLA) antigen, environmental factors or dietary habits. Further studies with HLA antigen typing in Saudi type 2 diabetics are needed to study this interesting observation. It has been shown in our study that autoimmune diabetes is more common in females, is significantly associated with younger age, lower BMI and shorter duration of diabetes, which is in agreement with other reports [30–33]. As observed by Gambelunghe et al. [25], our study shows no differences in the prevalence of ICA between diabetics and controls.

There is a well known association between type 2 DM and thyroid dysfunction. Smithson [8] reported an analysis of 206 diabetic patients. Screening revealed a prevalence of 5.5%. In a larger study that included 904 patients with type 2 DM, the prevalence was 10.9% in females and 6.9% in males [9]. Other reports investigated the prevalence of abnormal TSH concentration in type 2 DM, and it was found in 31% [10]. We reported thyroid dysfunction in 16% diabetics and it reaches 42% in LADA. Thyroid autoimmunity was commonly detected with thyroid dysfunction in LADA compared to type 2 diabetics and control. As observed by all the previous reports, our study showed that subclinical hypothyroidism and hypothyroidism were the commonest thyroid dysfunctions in diabetics. This could be related to the old age group of the samples studied.

It is clearly shown, in agreement with other reports, that thyroid autoimmunity and dysfunction are common in type 2 diabetics, especially autoimmune type. Symptoms of thyroid dysfunction are often insidious in onset and difficult to ascertain. Biochemical tests of thyroid functions are readily available and relatively inexpensive. Progression from subclinical disease to clinical disease has been observed in longitudinal studies [34]. The case for routine screening in type 2 DM is less clear than for type 1, although advocated by some authors [10]. Given the trend towards a younger onset of type 2 DM, further studies are needed to establish cost effectiveness of thyroid screening.

Conclusions

Thyroid dysfunction and autoimmunity are common in Saudi type 2 diabetics. Further studies are needed on the

cost effectiveness of screening for thyroid diseases in Saudi diabetics in addition to HLA gene typing of these patients for better understanding of this association.

Longitudinal studies are also needed on the effect of treatment of thyroid dysfunction on blood glucose control in diabetics.

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