ORIGINAL ARTICLE

Prevalence of Thyroid Autoantibodies in Type 2 Diabetic Patients

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ABSTRACT

OBJECTIVE: Due to the increased prevalence of thyroid dysfunction in subjects with type 2 diabetes and also this fact that antibodies could potentially identify subjects at risk of thyroid dysfunction, this study was conducted to investigate thyroid autoimmunity in type 2 diabetic patients**.**

MATERIAL AND METHODS: Among patients referred to Yazd Diabetes Research Center, 4000 type 2 diabetic patients were recruited and clinical examination was carried out and samples for thyroid function test including thyroxin (T4), triiodothyronine (T3), thyroid stimulating hormone (TSH), T3 resin uptake (T3RU), thyroid peroxidase antibodies (TPO-Ab) and thyroglobulin antibodies (Tg-Ab) were obtained.

RESULTS: Among 4000 type 2 diabetic subjects (1649 male and 2351 female), 1762(44%) were known to have thyroid disease. A total of 1466 (36.7%) had positive TPO antibodies and 1072 (26.8%) had positive Tg-Ab antibodies. The logistic regression of thyroid dysfunction on Tg-Ab as well as TPO-Ab status (positive vs. negative) was significant (P=0.0001).

CONCLUSION: Our results showed strong association of thyroid dysfunction with autoantibodies, especially in patients with Tg-Ab positive**.** Therefore, the findings suggest that all subjects with type 2 diabetes, particularly those with positive antibodies, should undergo annual screening to detect asymptomatic thyroid dysfunction.

KEY WORDS: Thyroid dysfunction, Type 2 diabetes, Thyroid peroxidase antibodies, Thyroglobulin antibodies.

INTRODUCTION

The prevalence of thyroid dysfunction rises with increasing age and in subjects with thyroid antibodies (1-4). The frequencies of thyroid autoantibodies are increased in type 1 diabetic patients with or without thyroid disorders and the presence of these autoantibodies in the latter group may predict the future development of thyroid dysfunction (5-7). The close association between thyroid autoantibodies, particularly thyroid microsomal or thyroid peroxidase antibodies (TPO-Ab) and autoantibodies to islet antigens, has been reported in type 1 diabetic patients (8-10).

It has been reported that the positivity to TPO-Ab antibodies in euthyroid subjects with type 1 diabetes predicts the progression to eventual hypothyroidism (10), whereas a few studies were conducted to evaluate thyroid autoimmunity in type 2 diabetic patients (11-14).

Due to the increased prevalence of thyroid

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dysfunction in subjects with type 2 diabetes (11,15,16), and this fact that antibodies could potentially identify subjects at risk of thyroid dysfunction, this study was conducted to investigate thyroid autoimmunity in type 2 diabetic patients.

MATERIALS AND METHODS

4000 patients with type 2 diabetes, involving 2351 females and 1649 males, who attended the diabetic clinic of Yazd Diabetes Research Center were studied. The criteria for eligibility included type 2 diabetes (according to ADA 2004) (17), absence of sever diabetes complications, hypercholesterolemia or medical conditions that can affect thyroid function. Subjects with secondary diabetes and those on medication that can affect thyroid function were excluded. The institution's Research Ethics Committee approval was obtained prior to study enrollment. Informed consent was obtained for all subjects and the cases of goiter, hyper – or hypothyroidism were noted. Clinical data of all patients which included sex, age at onset of diabetes, duration of diabetes, family history of diabetes and thyroid diseases, as well as a history of thyroid dysfunction, were obtained by reviewing the medical records and direct patient interview.

Laboratory Assessment:

Sera were obtained from all patients for the measurement of thyroglobulin antibodies (Tg-Ab) and thyroid peroxidase antibodies (TPO-Ab). Tg-Ab and TPO-Ab were measured by enzyme-linked immunosorbent assay (ELISA) method (Radin Co, Italy). TSH, T3 and T4 were measured by radioimmunoassay (RIA) method (Kavoshyar Co, Iran). The normal range was TSH: 0.25–4.00 mU/l, T4: 4.5-11 µg/dl, T3:70-204 ng/dl, TPO-Ab < 100 IU/ml, and Tg-Ab <100 IU/ml.

A patient was defined as hypothyroid if the TSH was more than 10 mU/l and/or if the patient had been on thyroxine therapy on the basis of raised TSH values documented earlier. Sub clinical hypothyroidism was defined as a normal free T4 in association with a raised TSH (3-10 mU/l) in subjects not on thyroxin therapy.

Statistical Analysis:

Statistical analyses were performed using SPSS for windows, version 13. Data are presented as mean±SD. Two unrelated samples were compared by student's t-test. A significant level of $P<0.05$ was used for univariate test. Logistic regression analysis was carried out to identify independent association of thyroid dysfunction, Anti TPO-Ab, and anti Tg-Ab.

RESULTS

There were 4000 type 2 diabetic patients enrolled in this study. The mean age of patients was 55.91±10.05 years and mean duration of diabetes was 11.72±6.78 years.

A total of 1466 (36.7%) participants had positive TPO antibodies (532 males, 934 females) (Table 1). Females were 0.72 times as likely to be TPO positive compared to males (95% CI: 0.63-0.72) ($P<0.001$). Similarly, the rate of thyroid dysfunction was higher in female subjects with positive TPO (63.7%) than males (36.2%) ($P<0.001$). Serum levels of TSH, T3 and T4 are presented in figures 1-3. according to TPO-Ab status of subjects.

The logistic regression of thyroid dysfunction on TPO status (positive vs. negative) was significant (likelihood ratio $\chi^2=546.28$, $P=0.0001$). TPO positive patients were 8.5

Table 1- Auto-antibodies Status in Patients Studied

	Anti-TPO Positive	Anti-TPO Negative	Anti-TG Positive	Anti-TG Negative
Graves' disease	191 (50.1%)	190 (49.9 %)	64 (16.8%)	317 (83.2%)
Hypothyroidism	542 (68.7%)	247 (31.3%)	205 (26%)	584 (74%)
Subclinical hypothyroidism	260(43.9%)	332 (56.1%)	72 (12.2%)	520 (87.8%)
Euthyroidism	473 (21.1%0	1765 (78.9%)	731 (32.7%)	1507 (67.3%)
Male	532 (32.26%)	1117 (67.73%)	449 (27.22%)	1200 (72.77%)
Female	934 (39.72%)	1417 (60.27%)	623 (26.49%)	1728 (73.51%)

times as likely to develop hypothyroidism (95% CI 7.12-10.28), 3.2 to develop subclinical hypothyroidism (95% CI 2.6-3.9), and 4.04 to develop hyperthyroidism (95% CI 3.22-5.08) (Figure 4).

The mean age of TPO negative subjects was 55.74±10.23 and for TPO positive subjects was 56.21±9.73 years (P= NS). There was a significant correlation between TPO-Ab, Tg-Ab, and TSH values (r=0.2, r=-0.05 respectively) (Figures 5,6). No significant correlation was seen between TPO-Ab and Tg-Ab with age, and diabetes duration (P=0.3 and P=0.7 respectively). There was no significant difference in TSH values between patients with positive TPO (28.01 ± 24.91 mU/l) and negative TPO (24.47 ± 24.66 mU/l) (P=0.06) on diagnosis of hypothyroidism.

The presence of Tg-Ab was associated with increased risk of thyroid dysfunction

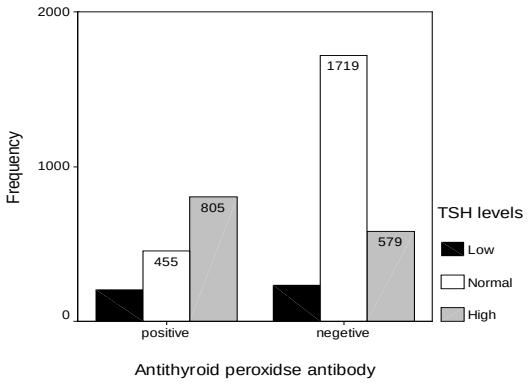

Figure 1- Distribution of Anti-TPO Antibody according to TSH Level

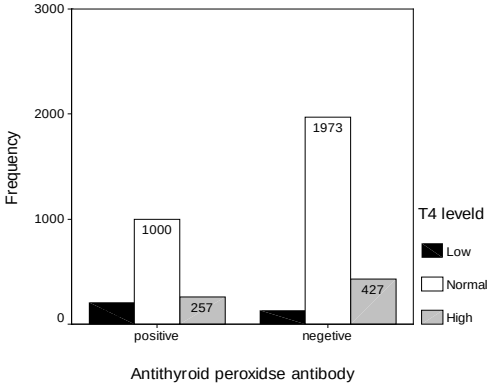

Figure 2- Distribution of Anti-TPO Antibody according to T4 Level

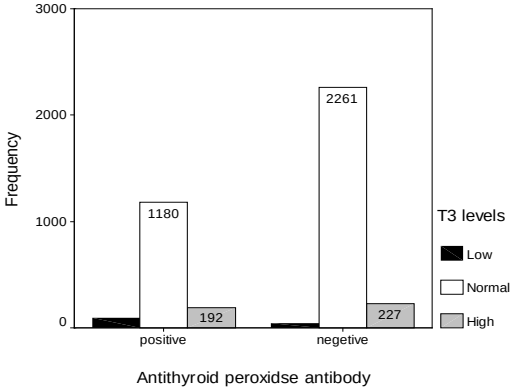

Figure 3- Distribution of Anti-TPO Antibody according to T3 Level

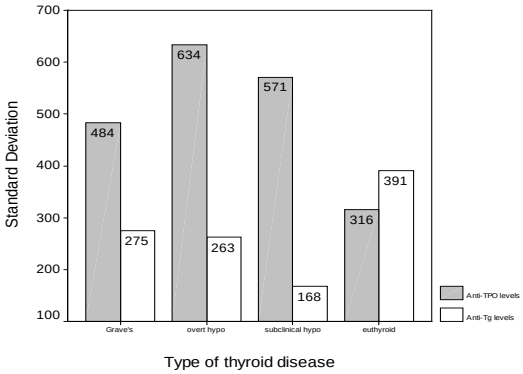

Figure 4- Anti-TPO and TG Antibodies in Type of Thyroid Diseases

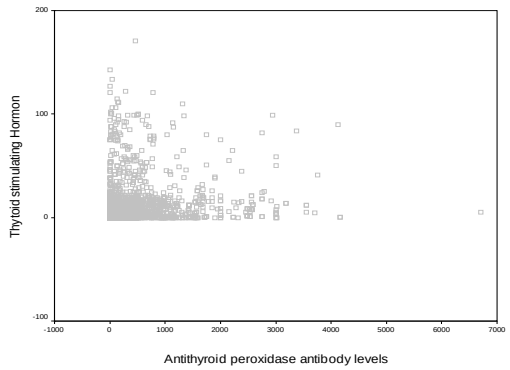

Figure 5- Correlation between Anti-TPO and TSH

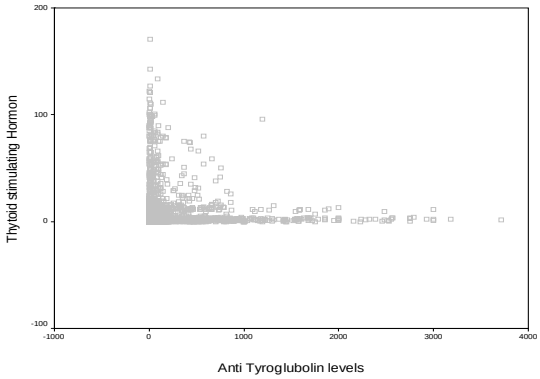

Figure 6- Correlation between Anti-TG and TSH

(likelihood ratio χ^2=121.24, P=0.0001): hyperthyroidism [OD, 0.36, (95 CI: 0.27-0.48)], hypothyroidism [OD, 0.59, (95 CI: 0.48-0.72)], and sub clinical hypothyroidism [OD, 0.25, (95 CI: 0.19-0.33)].

DISCUSSION

The study results showed a significant proportion of subjects with type 2 diabetes are positive for TPO-Ab (36.7%) and Tg-Ab (26.8%). Majority (67.7%) of these subjects with TPO-Ab have current evidence of thyroid dysfunction. 10.5% (420) of the subjects were both positive TPO-Ab and Tg-Ab. This suggests that there is much overlap between TPO-Ab and Tg-Ab. 18.8 percent of the subjects with thyroid dysfunction were positive for TPO-Ab but negative for Tg-Ab. This suggests that TPO-Ab measurement could pick up cases of thyroid dysfunction among type 2 diabetics, which could be missed by performing mere Tg-Ab.

21.1 percent of euthyroid patients were TPO-Ab positive, whereas 32.7% was Tg-Ab positive. It indicated that if we had used antibodies, as a single diagnostic tool in this study, we would have missed 16.8 percent of cases with thyroid dysfunction but with negative antibodies. Moreover, prevalence of positive Tg-Ab in euthyroid subjects was highest. It shows that Anti-Tg antibodies have a very low specificity in thyroid dysfunction diagnosis.

Some studies showed higher frequency of thyroid antibodies in patients with a longer duration of diabetes (18). Nevertheless in our study no statistically significant association was observed between TPO-Ab and diabetes duration.

Similar to other studies (6, 8, 10, 19), TPO-Ab was more frequent in females than in males in our study. The sex discrepancy may be related to effect of sex steroids on the immunoregulatory process (20). In addition, the prevalence of thyroid dysfunction was higher in women, especially those with positive TPO antibodies (21, 16).

Cross sectional studies have reported high prevalence of auto antibodies in type 2 diabetic patients compared with control group. In Radaideh's study, positive TPO antibodies were found in 8.3% of 650 type 2 diabetic patients vs. 10.3% of 282 control subjects. Positivity for both TPO-Ab and Tg-Ab was 2.5% in type 2 diabetics vs. 6% in control subjects (15).

Akbar et al studied 100 type 2 diabetics and 100 homogenous controls in regard to their age and sex. Thyroid autoimmunity was detected in 10% of diabetics vs. 5% in controls (11). In Yasmin's study TPO-Ab in type 2 diabetics was 42.3% vs. 12% in control group (14).

Other studies could not find any differences in autoimmunity in type 2 diabetic patients (13). In Ortega-Gonzalez's study, the frequency of TPO antibodies was similar in type 2 diabetic patients in comparison with healthy subjects (13).

In our study, in contrast to other studies (11, 15) prevalence of autoantibodies was very high .The reason for the higher prevalence is not known, but may be related to ethnic or geographical factors and laboratory assessment methods.

The NHANES III reported a prevalence of hypothyroidism in 4.6% and hyperthyroidism in 1.3% and a prevalence of positive TPO in 13% of the US population (22). In agreement with these findings, our results showed strong association of thyroid dysfunction with auto antibodies especially in patients with positive TPO-Ab. Patients with positive TPO-Ab were 5.22 times as likely to develop thyroid dysfunction. In our study, prevalence of hypothyroidism was significantly associated with positive TPO-Ab and Tg-Ab that such a relation was observed in Umpierrez's study (18). Further, sub clinical hypothyroidism has been shown to be associated with progression towards overt hypothyroidism in the general community (23, 24) and in diabetic patients (25). The risk is increased when thyroid antibodies are present (23). In Chubb's study sub clinical hypothyroidism was associated with TPO-Ab and age, but not with markers of glycemia (16). All these results show the

necessity of thyroid dysfunction screening in type 2 diabetic patients.

CONCLUSION

Our results suggest that all subjects with type 2 diabetes, particularly those with positive antibodies, should undergo annual screening to detect asymptomatic thyroid dysfunction. Also, further studies are required to compare thyroid antibodies in patients with diabetes as well as in the general population.

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REFERENCES

1. Eggertsen R, Petersen K, Lundberg PA, Nystrom E, Lindstedt G. Screening for thyroid disease in a primary care unit with a thyroid stimulating hormone assay with a low detection limit. British Medical Journal. 1988;297(6663):1586-92.
2. Cooper DS. Subclinical thyroid disease: a clinician's perspective. Ann Intern Med 1998;129: 135-8.
3. Sawin CT, Chopra D, Azizi F, Mannix JE, Bacharach P. The aging thyroid: increased prevalence of elevated serum thyrotropin levels in the elderly. JAMA: the journal of the American Medical Association. 1979;242(3):247-50.
4. Vanderpump MP, Tunbridge WM, French JM, Appleton D, Bates D, Clark F, et al. The incidence of thyroid disorders in the community: a twentyyear follow-up of the Whickham Survey. Clinical Endocrinology (Oxf) 1995;43(1):55-68.
5. Burek CL, Rose NR, Guire KE, Hoffman WH. Thyroid autoantibodies in Black and in White children and adolescents with type 1 diabetes mellitus and their first degree relatives, Autoimmunity 1990;7(2-3):157-67.
6. Lorini R, d'Annunzio G, Vitah L, Scaramuzza A. IDDM and autoimmune thyroid disease in the pediatric age group, Journal of pediatric endocrinology & metabolism: JPEM. 1996;9:89-94.
7. Lindberg B, Ericsson UB, Ljung R, Ivarsson SA. High prevalence of thyroid autoantibodies at diagnosis of insulin-dependent diabetes mellitus in Swedish children, Journal of Laboratory and Clinical Medicine 1997;130(6):585-9.
8. Groop L, Miettinen A, Groop PH, Meri S, Koskirnies S, Bottazzo GF. Organ-specific autoimmunity and HLA-DR antigens as markers for b-cell destruction in patients with type II diabetes, Diabetes 1988; 37: 99–103.
9. Verge CF, Howard NJ, Rowley MJ, Mackay IR, Zimmet PZ, Egan M, et al. Anti-glutamate decarboxylase and other antibodies at the onset of childhood IDDM: a population-based study, Diabetologia, 1994;37(11):1113-20.
10. Fernandez-Castaner M, Molina A, Lopez-Jimenez L, Gomez JM, Soler J. Clinical presentation and early course of type 1 diabetes in patients with and without thyroid autoimmunity, Diabetes Care ,1999;22(3):377–81.
11. Akbar DH, Ahmed MM, Al-Mughales J. Thyroid dysfunction and thyroid autoimmunity in Saudi type 2 diabetics. Acta Diabetologica. 2006;43(1):14-8.
12. Kasim S, Bessman A. Thyroid autoimmunity in type 2 (non-insulin-dependent) diabetic patients of Caucasoid, black and Mexican origin. Diabetologia. 1984;27(1):59-61.
13. Ortega-González C, Liao-Lo A, Ramírez-Peredo J, Cariño N, Lira J, Parra A. Thyroid peroxidase antibodies in Mexican-born healthy pregnant women, in women with type 2 or gestational diabetes mellitus, and in their offspring. Endocr Pract. 2000;6(3):244-8.
14. Yasmin T, Ghafoor F, Malik T, S RN, Khan AU. Pattern of thyroid autoimmunity in type 1 and type 2 diabetics. J Coll Physicians Surg Pak. 2006;16(12):751-4.
15. Radaideh AR, Nusier MK, Amari FL, Bateiha AE, El-Khateeb MS, Naser AS, Ajlouni KM. Thyroid dysfunction in patients with type 2 diabetes mellitus in Jordan: Saudi Med J. 2004;25(8):1046-50.
16. Chubb Blac SAP, Davis WA, Inman Z, Davis TME. Prevalence and progression of subclinical hypothyroidism in women with type 2 diabetes: the Fremantle Diabetes Study. Clinical Endocrinology 2005;62 (4): 480-6 .
17. American Diabetes Association.. Standard of medical care in diabetes. Diabetes care 2004; 27(supp 1): S15-S34.
18. Umpierrez GE, Latif KA, Murphy MB, Lambeth HC, Stentz F, Bush A, et al. Thyroid dysfunction in patients with type 1 diabetes: a longitudinal study Diabetes Care. 2003;26(4):1181-5.
19. Chang CC, Huang CN, Chuang LM. Autoantibodies to thyroid peroxidase in patients

with type 1 diabetes in Taiwan, European journal of endocrinology. 1998;139(1):44-8.
20. Farid N.R. Immunogenetics of autoimmune thyroid disease, Endocrinology and metabolism clinics of North America 1987;16(2):229-45.
21. Perros P, McCrimmon RJ, Shaw G , Frier BM. Frequency of thyroid dysfunction in diabetic patients: value of annual screening. Diabetic Medicine, 1995; 12(7): 622–7.
22. Hollowell JG, Staehling NW, Flanders WD, Hannon WH, Gunter EW, Spencer CA, Braverman LE: Serum TSH, T4, and thyroid antibodies in the United States population (1988–1994): National Health and Nutrition Examination Survey (NHANES III). J Clin Endocrinolo Metab, 2002: 87:489–99.
23. Vanderpump MPJ, Tunbridge WMG, French JM, Appleton D, Bates D, Clark F., et al. The incidence of thyroid disorders in the community: a twenty-year follow-up of the Whickham survey .Clinical Endocrinology, 1995; 43(1): 55–68.
24. Parle JV, Franklyn JA, Cross KW, Cross SC, Sheppard MC. Prevalence and follow-up of abnormal thyrotrophin (TSH) concentrations in the elderly in the United Kingdom. Clinical Endocrinology, 1991 ;34(1):77–83.
25. Gray RS., Borsey DQ., Irvine WJ., Seth J, Clarke BF. Natural history of thyroid function in diabetics with impaired thyroid reserve: a four year controlled study. Clinical Endocrinology, 1983;19(4):445-51

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