ORIGINAL ARTICLE ASIAN JOURNAL OF MEDICAL SCIENCES

Prevalence of thyroid dysfunction in patients with Type 2 diabetes mellitus and its correlation with insulin resistance and serum markers for autoimmune thyroiditis

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Submitted: 29-05-2015 Revised: 28-06-2015 Published: 01-07-2015

ABSTRACT

Background: The term "THYROID DIABETES" was coined in early literature to depict the influence of thyroid hormone excess in deterioration of glucose control. Although autoimmune thyroid disease is more prevalent in Type1 Diabetes mellitus as a result of their common origin, the prevalence of hypothyroidism and hyperthyroidism is supposed to be similar to that of general population in patient with type2 DM. The purpose of the study was to evaluate the prevalence of thyroid dysfunction in patients with type2 diabetes mellitus and to correlate thyroid abnormalities with insulin resistance and serum markers for autoimmune thyroiditis. **Methods:** 120 cases of type2 diabetes mellitus patients satisfying WHO criteria without pre-existing thyroid disease were included in the study. Thyroid function test, fasting serum insulin was done.HOMA-IR & HOMA-B (HOMA-Homeostatic model assessment) was calculated. Serum antithyroid peroxidase anibody (anti-TPO) and antithyroglobulin antibodies (anti-TG) and ANA were done. **Results:** Prevalence of thyroid dysfunction in type2 diabetes mellitus was 28.33% according to our study, which included overt hypothyroidism (15%), subclinical hypothyroidism (8.33%), secondary hypothyroidism (0.83%), overt hyperthyroidism (1.67%) and subclinical hyperthyroidism (2.5%). Anti TPO and anti TG antibodies were elevated in 62.07% cases of hypothyroidism, 40% cases of hyperthyroidism and 6.9% euthyroid cases of type2 DM. Anti TPO and antiTG antibodies were significantly raised in type2DM patient with hypothroidism than that of euthyroid (p value <0.0001).Compared to euthyroid diabetics, hypothyroid cases had lower values of insulin resistance markers like fasting insulin, HOMA-IR and HOMA-B. Hyperthyoid cases had higher values. **Conclusion:** Hyperthyroid diabetics have higher insulin resistance as fasting insulin, HOMA-IR, HOMA-B showed negative correlation with TSH. (p value <0.05).

Access this article online

Website: http://nepjol.info/index.php/AJMS

DOI: 10.3126/ajms.v6i6.12603

Key Words: Thyroid diabetes, autoimmune thyroid disease, anti thyroid peroxidase antibody, Homeostatic model assessment for insulin resistance.

INTRODUCTION

The term "THYROID DIABETES" was coined in early literature to depict the influence of thyroid hormone excess in deterioration of glucose control. Although autoimmune thyroid disease is more prevalent in Type1 Diabetes mellitus as a result of their common origin, the prevalence of hypothyroidism and hyperthyroidism is supposed to be similar to that of general population in patient with type2 DM. Glucose intolerance is associated

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with hyperthyroidism. Hypothyroidism is characterized by insulin resistance.[1] In type2 DM patients the presence of highly frequent subclinical forms of hyperthyroidism and hypothyroidism should be ruled out since they may be associated with increased risk of nephropathy, retinopathy and cardiovascular events.[2] The prevalence of subclinical hypothyroidism is higher in patients with metabolic syndrome which can be explained by concomitance of deranged serum lipid concentration, obesity, hypertension, insulin resistance in both these conditions.[3]

Prevalence of Diabetes mellitus in South-East Asia is 8.3% according to international Diabetes federation.75 million people have Diabetes.In other words 1 in 12 adults are suffering from Diabetes mellitus. Total Diabetes related deaths are estimated to be 1185.2 thousands in 2014.[4]

According to the Whickham survey, thyroid dysfunction affected 6.6% of adults (Tunbridge, et al. 1997).[5] The reported prevalence of thyroid dysfunction in diabetes varied from 2.2 to 17% in these different works. However, little is known about thyroid size and structure in type2 diabetes mellitus (Junik et al. 2006).[6] Although several studies have shown the association between thyroid autoimmunity and type-1 diabetes (Park, et al. 2000; Menon, et al. 2001)[7,8] little is known of the risk of thyroid autoimmunity in subjects with type-2 diabetes (Matejkova-Behanova, et al. 2002).[9] Studies of Perros et al showed a prevalence of 13.4% and that of Papazafiropoulou 12.3%.[10] A recent study in Tumkur, Karnataka showed the prevalence of hypothyroidism in Diabetes mellitus was 12.06%.[11]

Thyroid hormone act differentially in liver, skeletal muscle and adipose tissue-the main targets of insulin action. While Thyroid hormones oppose the action of insulin and stimulate hepatic gluconeogenesis and glycogenolysis[12,13] they upregulate the expression of genes such as GLUT-4 and phosphoglycerate kinase involved in glucose transport and glycolysis respectively, thus acting synergistically with insulin facilititating glucose disposal and peripheral utilisation.[14,15]

In hypothyroidism, glucose homeostasis is also affected although its clinical impact is less obvious. Decreased glucose disposal (as compared with euthyroid subjects) has been proved in hypothyroid patients by different methods including clamp studies.[16,17] Hypothyroidism results in unimpaired[18] or decreased[19,20] liver glucose output thereby compensating for insulin resistance present in peripheral tissues and accounting for the diminished insulin requirement for glycaemic control in hypothyroid diabetic patients.

Aims and objectives

1. To Study the prevalence of thyroid dysfunction in patients with type 2 Diabetes mellitus.
2. Correlation of thyroid abnormalities with Insulin resistance and serum markers for autoimmune thyroiditis.

MATERIALS AND METHODS

Case Selection

One hundred twenty consecutive cases of type2 diabetes mellitus patients satisfying WHO (World Health Organisation) criteria without pre-existing thyroid disease attending Medicine Outpatient Department or admitted in department of medicine between September 2012 to September 2013 were taken as cases. Detailed history taking and clinical examination were done in all cases. Thyroid function test including T3,T4,TSH was done by RIA method (IMMUNOTECH).

Fasting serum insulin was done.HOMA-IR & HOMA-B was calculated as:

$$\text{HOMA-IR} = [\text{FPG(mg/dl)} \times \text{Fasting Insulin}(\mu\text{U/ml})]/405$$

$$\text{HOMA-B} = [360 \times \text{Fasting Insulin}(\mu\text{U/ml})]/[\text{FPG(mg/dl)} - 63]$$

Serum autoimmune markers like ANA, anti thyroid peroxidase anibody (anti-TPO) and antithyroglobulin antibodies (anti-TG) were done.

RESULTS

According to our study, prevalence of thyroid dysfunction in patients with type2 DM was 28.33 % (34 out of 120 cases) as shown in (Figure 1). Among these 34 cases, 29(24.17%) were hypothyroid and 5(4.16%) were hyperthyroid. 86 out of 120 cases(71.67%) were euthyroid.

Out of 120 cases of Type2 diabetes mellitus, 66 were males (55%) and 54 were females (45%).Out of 29 hypothyroid diabetic cases 19 were females and 10 were males as shown in (Figure 2). Out of 5 cases of hyperthyroidism,3 were females and 2 were males.

Out of 29 cases of hypothyroid diabetics,overt hypothyroidism was found in 18(15%) patients, subclinical hypothyroidism in 10(8.33%) cases and secondary hypothyroidism in 1(0.83%) cases. Among 5 cases of hyperthyroidism, 2(1.67%) were overt and 3(2.5%) were subclinical as shown in (Figure 3). Twenty-three cases (19.17%) were found to have sick euthyroid syndrome.63(52.5%) patients were euthyroid. So overt hypothyroidism was the major thyroid abnormality in

type2 DM followed by subclinical hypothyroidism according to our study.

Anti-TPO antibodies were found to be positive in 18(62.07%) out of 29 cases of type2 DM with hypothyroidism, 2(40%) out of 5 cases of hyperthyroid and 6(6.97%) out of 86 cases of euthyroidism as shown in (Figure 4). These euthyroid diabetic patients with anti TPO antibodies are at risk of developing autoimmune thyroiditis in future. Autoimmune thyroid disease is characterized by lymphocytic infiltration.TPO antibodies are an early sign of lymphocytic infiltration and they can be used as a predictor for the future development of hypothyroidism. In the 20-year follow-up study of the Wickham survey,the presence of TPO antibodies in females with a normal TSH level confined an annual risk of developing overt hypothyroidism of 2.1%.21 This correlated with the antibody titre: if TPO antibodies were negative the risk was 4%,if weakly positive 23%,if moderately positively 33%,and if strongly positive the risk increased to 53%.

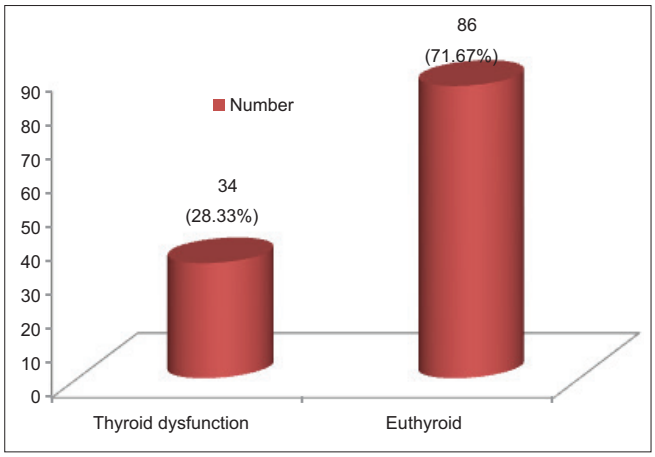

Figure 1: **Prevalence of Thyroid dysfunction in Type 2 DM**

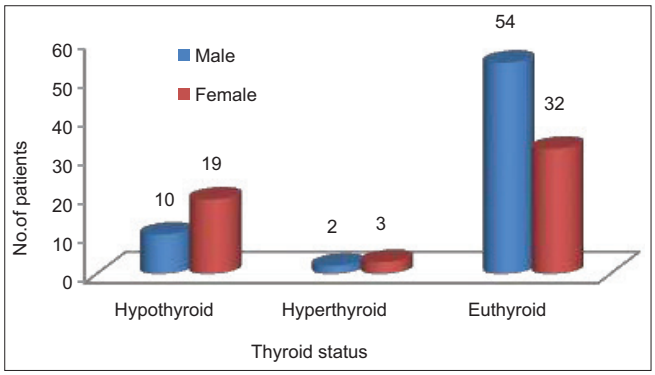

Figure 2: **Gender distribution in type2 DM with thyroid dysfunction**

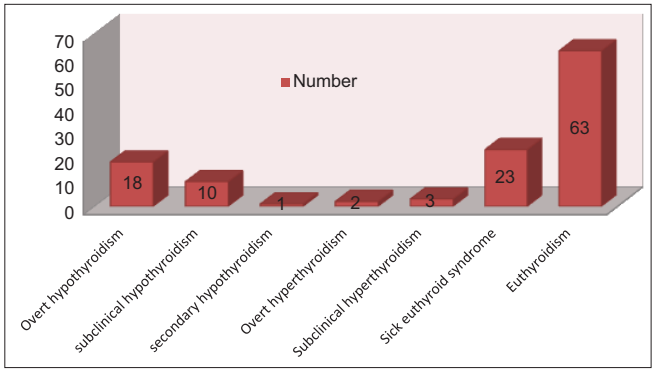

Figure 3: **Categories of thyroid dysfunction in Type2 DM**

Regression analysis showed that TSH was positively correlated with anti TPO antibody(r=0.4927) and the association was extremely significant (p<0.0001) as shown in (Table 1).

Pearson's correlation showed that, there was a significant negative correlation between TSH and fasting serum insulin, HOMA-IR and HOMA-B (p<0.05) as shown in (Table 2). It means high TSH was associated with low insulin resistance markers and low TSH was associated with higher insulin resistance and β-cell function.

The levels of T3 ,T4 were lower and TSH,anti TPO,antiTG & ANA were significantly higher(p<0.05) in hypothyroid

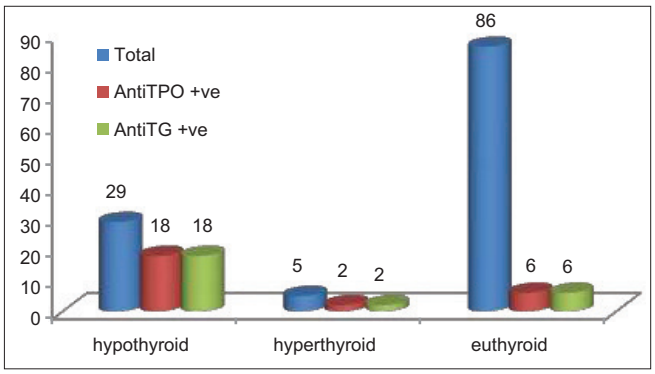

Figure 4: **Presence Of Anti-TPO& Anti-TG Antibodies In Type2 DM With Thyroid Dysfunction**

Table 1: Correlation between TSH and anti-TPO antibody

Parameters	TSH	Anti-TPO	p value
Mean	6.29	55.33	<0.0001
Median	2.3	20	Extremely
SD	16.016	110.37	Significant

Table 2: Correlation between and fasting, Insulin, HOMA-IR and HOMA-B

	r value	p value	Significance
TSH vs fasting insulin	−0.29	0.0009	Extremely significant
TSH vs HOMA-IR	−0.21	0.0179	Significant
TSH vs HOMA-B	−0.2451	0.007	Very significant

diabetic subjects than in euthyroid subjects.They had significantly lower values of fasting serum insulin,HOMA-IR,HOMA-B than that of euthyroid as shown in (Table 3). Compared to euthyroid,hypothyroid diabetics were older in age.(p :0.0294).Neither hypothyroid nor hyperthyroid subjects showed significant difference in FBS,2hrPPBS,HbA1C,lipid profile

DISCUSSION

Prevalence of thyroid dysfunction in type2 diabetes mellitus was 28.33% according to our study, which included overt hypothyroidism (15%), subclinical hypothyroidism (8.33%),secondary hypothyroidism(0.83%), overt hyperthyroidism(1.67%) and subclinical hyperthyroidism(2.5%) as shown in (Figure 3). Recently a prevalence of 12.3% was reported among Greek diabetic patients by Papazafiropoulou et al 2010.[11] In another study done by Gang Chen et al (2010), thyroid dysfunction was observed in 12.1% diabetic patients. Palma et al (2013) found that prevalence of thyroid dysfunction in type 2 DM was 13.11%. A retrospective study of thyroid dysfunction in type2 diabetes mellitus revealed prevalence of 31.2% (Demitrost L et al).[22]

Bassyouni et al (2010) found a higher prevalence of thyroid dysfunction in older subjects with type 2 DM. Our study also revealed an increase in thyroid dysfunction with increasing age up to 69 year after which it decreased.

Anti TPO and anti TG antibodies were elevated in 62.07% cases of hypothyroidism, 40% cases of hyperthyroidism and 6.9% euthyroid cases of type2 DM as shown in (Figure 4). Anti TPO and anti-TG antibodies were significantly raised in type 2 DM patient with hypothroidism than that of euthyroid (p value<0.0001).

Table 3: Comparison between hypothyroidism and euthyroidism

Parameters	Euthyroidism (n=86)	Hypothyroidism (n=29)	P value
Age (years)	60.96±14.47	62.03±13.2	0.0294
FBS	222.59±108.6	220.49±133.1	0.448
2hr PPBS	280.18±104.33	273.53±144.74	0.4509
HbA1c	8.57±1.38	8.46±2.02	0.4384
TC	168.6±54.92	179.65±56.79	0.1552
TG	166.13±113.08	222.14±178.41	0.0544
HDL	40.78±11.04	38.96±8.32	0.3251
LDL	10232.31	109.34±36.24	0.0726
VLDL	27.29±11.97	25.1±10.22	0.2236
TSH	2.01±1.23	20.03±28.87	<0.0001
T3	0.83±0.49	0.7±0.5	0.0087
T4	8.36±22.16	4.192.29	0.0002
TPO Ab +ve	36.34±90.6	106.49±145.5	<0.0001
TG Ab +ve	151.66±199.53	384.41±260.85	<0.0001
ANA	0.54±0.94	1.47±2.05	<0.0001
Fasting insulin	25.33±13.14	17.16±14.16	0.0044
HOMA-IR	14.03±10.43	12.18±18.52	0.006
HOMA-B	89.91±112.84	57.45±77.87	0.0043

Compared to euthyroid diabetics, hypothyroid cases had lower values of insulin resistance markers like fasting insulin, HOMA-IR and HOMA-B as shown in (Table 3). Hyperthyoid cases had higher values. It signifies that hyperthyroid diabetics have higher insulin resistance. Fasting insulin, HOMA-IR, HOMA-B showed negative correlation with TSH (p value<0.05).

The insulin levels were increased in this study partly because of increased glucose-stimulated insulin secretion (GSIS). Another important reason for the increase was insulin resistance which is common in hyperthyroidism. In hyperthyroidism, pancreatic β-cells secrete more insulin to compensate for the increased demand of insulin when plasma glucose increases and IR exists, which leads to an apparent increase in β-cell secretory function (a higher HOMA-β) in this study.

However in this study, we did not find the evidence of impaired β-cell function in hyperthyroidism which may be explained by compensatory hyperfunction of β-cell. As reported in a recent follow-up study, HOMA β-cell function increased between 3 and 4 years before diagnosis and then decreased until diagnosis of diabetes, which suggested that it would take several years before the impairment of β-cell function. As hyperthyroid subjects were diagnosed recently, so the course of thyroid disorder was not long enough to impair β-cell function.

In most other studies, the concentration of insulin in hypothyroidism is reported to be normal[23] or decreased, [24,25] which is similar to our result. In hypothyroidism, glucose homeostasis is affected due to reduced intestinal glucose absorption, hepatic gluconeogenesis and glycogenolysis and peripheral tissue glucose disposal.

Insulin sensitivity in hypothyroid patients has been found to be normal or decreased. Hypothyroidism, even in the subclinical stage, has been shown to be associated with insulin resistance.[3,26] Our findings were different from these studies. A significant lower HOMA-IR (associated with a lower HOMA- β) was observed when we analyzed the participants with markedly elevated TSH levels suggesting that insulin sensitivity was increased in this group. Only two studies reported an increased sensitivity of glucose disposal to insulin in hypothyroidism,[27] which was somewhat similar to this study.

In order to further understand the relationship between thyroid function, insulin resistance and insulin secretion

of β-cells, a multivariate linear regression analysis with HOMA-IR or HOMA- β as the outcome was used. We found a significant negative correlation between TSH and IR assessed by HOMA-IR index, which was contrary to other studies.[28,29,30] In a trial with thyroid hormones in obesity, a positive correlation between IR parameters and serum TSH was significantly influenced by the BMI.[30] In fact, most of the IR parameters were related to obesity and dyslipidemia. Some studies also suggested that thyroid function might cause dyslipidemia through altered insulin sensitivity in healthy subjects[31] and patients with type2 diabetes mellitus.[32] However, we found that HOMA-IR was diminished in the group with serum TSH>10μU/ml, even though TG, LDL levels were significantly higher in this group suggesting that obesity and dyslipidemia in hypothyroidism were not associated with IR in this study.

There are some other mechanisms that may be responsible for these observations. Generally, there is a negative correlation between TSH and thyroid hormones. The higher serum TSH usually means the lower thyroid hormones via negative feedback. HOMA-IR decreased as TSH increased, which may be interpreted as a negative correlation between insulin sensitivity and thyroid hormones. It is well known that thyroid hormones have insulin antagonistic effects. As TSH increased, thyroid hormones decreased and insulin antagonistic effects weakened. It may be the main mechanism for these results. Besides, it is also possible that the course of thyroid disorder in this study was not long enough to impact the insulin sensitivity in hypothyroidism. On the other hand, the negative correlation between serum TSH and HOMA-β in this study could be interpreted as an influence of the altered insulin sensitivity on the secretion of β-cells.

CONCLUSION

The prevalence of thyroid dysfunction in type2 diabetes mellitus was 28.33% according to our study. The most common thyroid abnormality was overt hypothyroidism (15%). Anti TPO and anti-TG antibodies were positive in 62.07% cases of hypothyroidism and 40% cases of hyperthyroidism. TSH showed significant positive correlation with anti TPO and anti-TG antibodies ($p<0.0001$). Our study demonstrated significant negative correlation between TSH and indices of insulin resistance and beta cell function (HOMA-IR, HOMA-B)[$p<0.05$].

ABBREVIATIONS

ANA-antinuclear antibody,DM-Diabetes mellitus, FPG-Fasting plasma glucose,GLUT: Glucose transporter, HbA1c-Glycosylated haemoglobin, HOMA-IR-homeostatic model assessment for insulin resistance, HOMA-B-homeostatic model assessment for beta cell function, RIA-radioimmuno assay, TH-Thyroid Hormone, TSH-Thyroid stimulating hormone, TPO-thyroid peroxidise, TG-thyroglobulin.

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Authors Contribution:
SS: Conception and design, acquisition of data. **SKD:** Analysis and interpretation of data. **SSK:** Drafting the article, Critical revision of the article. **MMN:** Critical revision of the article. **PK:** Conception and design, acquisition of data. **UD:** Critical revision of the article, final approval of the version to be published.

Source of Support: Nil, **Conflict of Interest:** None declared.