Original Article

Thyroid Status in Patients with Type 2 Diabetes Attending a Tertiary Care Hospital in Eastern India

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Abstract

Objective: Type 2 diabetes mellitus and thyroid dysfunction (TD) are two major public health endocrine problem, but the prevalence of TD and iodine status in patients with T2 DM in India is less studied. The study objective was to explore the prevalence of TD and to evaluate iodine health in type 2 diabetes patients attending a tertiary care center in Eastern India. **Methods:** Consecutive 100 patients with diabetes attending outpatient department were evaluated clinically and biochemically (thyrotropin [TSH], free thyroxine, anti-TPO antibody, and urinary iodine). We excluded pregnant women or patients taking drugs that can alter thyroid function. Subclinical hypothyroid and overt hypothyroidism were diagnosed as per standard definitions. **Results:** Out of 100 patients were analyzed, 51 (51%) were male. Mean (±standard deviation) age was 45.4 ± 11.2 years, body mass index 24.1 ± 4.28 kg/m^2, and duration of diabetes 7.76 ± 5.77 years. The prevalence of subclinical hypothyroidism and overt hypothyroidism was 23/100 (23%) and 3/100 (3%), respectively. Thyroid autoantibody was positive in 13 (13.1%) patients. All patients were iodine sufficient. A trend toward increased neuropathy ($r = 0.45$) and nephropathy ($r = -0.29$) was associated with rising TSH. **Conclusion:** Almost one in four people living with diabetes are suffering from TD. Thus, routine screening should be implemented. Salt iodination program is a huge success in this part of the country.

Keywords: Diabetic peripheral neuropathy, electrochemical skin conductance, normative data, sudomotor function

Introduction

The association between type 2 diabetes mellitus (T2DM) and thyroid dysfunction (TD) has been reported in medical literature since 1979.[1] Many studies have reported varying prevalence (10%–24%) of TD in T2 DM.[2] This could partially be due to variation in autoimmunity and iodine status. A previous study from India[3] suggested a thyroid disease prevalence of 31.2% among T2 DM patients. The implication of TD on diabetes-related complications or cardiovascular risks is less documented. Iodine status in diabetic individuals in India has not been reported.

Methods

We conducted an observational cross-sectional study. Consecutive one hundred patients with diabetes who attended our out-patient clinic were evaluated. Diabetes was defined as per the American Diabetes Association criteria (Fasting plasma sugar ≥126 mg/dl, postprandial blood sugar ≥200 or Glycated hemoglobulin [HBA1c] ≥6.5% on 2 occasions). Those patients were on treatment for diabetes as well as for their co-existing comorbidities. Written informed consent for the study was obtained from all the patients. We excluded pregnant women and those taking glucocorticoid or amiodarone.

All patients underwent clinical evaluation, followed by laboratory evaluation. The following clinical variables were documented: gender, age (years), duration of DM (years), body mass index (BMI), blood pressure (systolic and diastolic), monofilament test (MFT), ankle brachial index, goiter, acanthosis nigricans, and ankle jerk. History of diabetes and thyroid disease in family and addiction history was documented. Fundus photography was taken by optometrist and retinopathy staging was done as per Early Treatment

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Diabetic Retinopathy Study (ETDRS) Research Group diabetic retinopathy classification system. Blood samples were obtained for biochemical analysis: HbA1c, lipid profile, creatinine, free thyroxine (FT4) and thyrotropin (TSH), anti-thyroperoxidase antibody (anti-TPO), urine for the albumin-creatinine ratio (ACR) and urinary iodine. HBA1c was measured by high-pressure liquid pressure chromatography Biorad D10 method. Serum TSH, FT4, and anti-TPO were estimated by the electrochemiluminescence technique using commercially available kits from Siemens Diagnostics (Mannheim, Germany) with Immulite 1000 analyzer. The analytical sensitivity and total precision values for TSH and FT4 assays were 0.004 μIU/ml and 2.2%, 0.35 ng/dl and 2.7%, respectively. The laboratory reference ranges were TSH (0.4–4 μIU/ml) and FT4 (0.8–1.9 ng/dl) and the inter-assay coefficients of variation (CV) for the assays were 8.9% and 5.5%, respectively. The corresponding values for inter-assay CV, total precision and analytical sensitivity for anti-TPO were 10.5%, 7.6%, and <7 IU/ml. Urinary iodine was measured using Sandell-Kolthoff method (normal range >100 μg/L).

TD was classified as clinical hypothyroidism (C-Hypo) if TSH levels were >4 μIU/mL and FT4 levels were lower than 0.8 ng/dL; sub C-Hypo (SC-Hypo) if TSH levels were >4 μIU/ml and FT4 levels ranged from 0.8 ng/dl to 1.9 ng/dL, SC-Hyper if TSH levels was lower than 0.4 μIU/ml and FT4 levels ranged from 0.8 to 1.8 ng/dL and clinical hyperthyroidism (C-Hyper) if TSH levels were lower 0.4 μIU/ml and FT4 levels were higher than 1.9 ng/dL. Anti-TPO levels >35 IU/mL was considered to be positive and suggested autoimmunity.

Statistical analysis

Statistical Package for the Social Sciences (version 14.0, SPSS Inc., Chicago, IL, USA) was used for data processing and analysis. Results on continuous measurements were presented on Mean ± standard deviation and results on categorical measurements were presented in number (N) and percentage (%). Spearman Correlation coefficient was done between TSH and other variables.

Results

Overall 100 patients were included in the final analysis. The demographic and clinical data are presented in Table 1. Out of 100 patients, 51 were male, mean age was 51.4 ± 11.2 years and mean BMI was 24.1 ± 4.28 kg/m^2. The average duration of diabetes was 7.76 ± 5.57 years and mean HBA1c was 8.18 ± 1.67%. Only 29% of patients had HbA1c below 7%.

Positive family history of diabetes was found in 62 patients and that of thyroid only in 3 patients. Overall 19 patients had an addiction with tobacco (chewable 12, smoking 10, both 3), whereas addiction to alcohol was found only in 11 patients. Clinically 43 patients had features of insulin resistance (Acanthosis nigricans), and 5 patients had a goiter. Comorbidities included hypertension (55%) and dyslipidemia (91%), yet only 45% and 27.4% of them were on treatment. Prevalence of diabetes complications were as follows: distal symmetrical peripheral neuropathy 19% (as measured by MFT), moderately increased proteinuria 34%, severely increased proteinuria 8% (defined as urinary albumin to creatinine ratio 30–300 and >300 mg/g, respectively), retinopathy mild 8% and moderate 2% (as per ETDRS Research Group diabetic retinopathy classification system).

Out of 100 patients, 74 (74%) were euthyroid, subclinical hypothyroid (SC-Hypo) was present in 23 (23%) (one on treatment), and overt hypothyroidism (C-Hypo) was present in 3 (3%) patients (two on treatment). None of the patients was suffering from subclinical or clinical hyperthyroidism. Anti-TPO antibody was positive in 13 (13%) patients. None of the patients had low urinary iodine. Tables 2 and 3 summarize the TD and iodine deficiency in our cohort. TSH had a significant positive correlation with vibration perception threshold (P = 0.01, r = 0.45) and significant negative correlation with estimated GFR (eGFR) (P = 0.045, r = −0.29) [Table 4]. TSH did not have a significant correlation with urine ACR or retinopathy.

Discussion

Thyroid hormone itself affects intermediatory metabolism and thus alter glucose homeostasis. Hypothyroidism leads to reductions in hepatic glucose output, gluconeogenesis, and peripheral glucose utilization thus predisposing to hypoglycemia.[4] Use of medications for diabetes also alters thyroid function. For example, use of metformin has been

Table 1: Clinical and demographic data of the studied population

Characteristics (n=100)	Values
Age (years)	45.4±11.2
Sex male:female	51:49
BMI (kg/m^2)	24.1±4.28
Duration of diabetes (years)	7.76±5.77
Family history of diabetes/thyroid (%)	62/3
Addiction smoking/alcohol (%)	19/11
Goiter (1B or more) (%)	5
Acanthosis nigricans	43
Grade I	30
Grade II	11
Grades III	2
Retinopathy (ETDRS Classification) (%)	
Mild NPDR	8
Moderate NPDR	2
Diatal symmetric neuropathy (%)	19
Nephropathy albuminuria	
Moderate	34
Severe	8
HbA1c (%)	8.18±1.67
Hypertension (%)	55
Dyslipidemia (%)	91

BMI: Body mass index, ETDRS: Early Treatment Diabetic Retinopathy Study, NPDR: Nonproliferative diabetic retinopathy, HbA1c: Glycated hemoglobin

Table 2: Prevalence of thyroid dysfunction in type 2 diabetes

Thyroid function (*n*=100)	*n* (%)
Euthyroid	74 (74)
SC-hypo	23 (23)
C-hypo	3 (3)
SC-hyper	0
C-hyper	0

SC-hypo: Subclinical hypothyroidism, C-hypo: Clinical hypothyroidism, SC-hyper: Subclinical hyperthyroidism, C-hyper: Clinical hyperthyroidism

Table 3: Prevalence of thyroid autoimmunity and iodine deficiency in type 2 diabetes

Parameters (*n*=100)	*n* (%)
Anti TPO antibody positivity	13 (13)
Low urinary iodine (<100 µg/L)	0

TPO: Thyroid peroxidase

Table 4: Correlation between thyroid stimulating hormone and diabetic complications

Correlation between TSH and diabetic complications	With VPT	With urine ACR	With eGFR	With retinopathy
P	0.01	0.10	0.045	0.44
Coefficient of correlation (*r*)	0.45	0.16	−0.29	0.07

TSH: Thyroid stimulating hormone, VPT: Vibration perception threshold, ACR: Albumin creatinine ratio, eGFR: Estimated GFR

shown to cause TSH suppression in patients receiving levothyroxine[5] and insulin increases the level of FT4 while suppresses the level of T3 by inhibiting the hepatic conversion of T4 to T3.[6] Worldwide there is variation in prevalence of TD, possibly due to differing iodine and autoimmunity status. Interestingly, none of our patients were suffering from Iodine deficiency. The study result is consistent with the WHO statement[7] in 2004 that India has gained optimal Iodine nutrition although few studies[8,9] form our state revealed inadequate iodine concentration in salt in 20%–32% of samples at the consumer level. The prevalence of thyroid autoimmunity was 13% among people with diabetes in our study.

Multiple studies revealed the increased prevalence of TD in type 2 diabetics. A recent meta-analysis[10] of 61 studies performed worldwide described adjusted pooled prevalence of SC-Hypo in T2DM patients was 10.2%. Meanwhile, T2DM was associated with a 1.93-fold increase in the risk of SC-Hypo (95% confidence interval [CI]: 1.66, 2.24). However, the studies from India showed the much higher prevalence of TD. For example, Gurjeet[11] reported 15% prevalence of sC-Hypo in type 2 diabetics in Punjab; Demitrost[3] from Manipur reported the same to be 16.3%; Anil *et al*.[12] from South India found this prevalence to be 11.25% and recently Chaturvedi *et al*.[13] from Meerut reported this prevalence as high as 27%. Most of the studies[11-13] from India also reported the prevalence of subclinical hypothyroid is higher in diabetics as compared with nondiabetics. The study describes 23% prevalence of SC-hypo in people with diabetes. This is consistent with the results of previously published reports. We did not have any control arm.

Results from previous meta-analysis[10] reported SCH might affect the development of diabetic complications with an overall odds ratio of 1.74 (95% CI: 1.34, 2.28) for diabetic nephropathy, 1.42 (95% CI: 1.21, 1.67) for diabetic retinopathy, 1.85 (95% CI: 1.35, 2.54) for peripheral arterial disease, and 1.87 (95% CI: 1.06, 3.28) for diabetic peripheral neuropathy. We found a trend toward higher diabetic complications (neuropathy and nephropathy) with rising TSH. However, we did not find any difference in diabetes-related complications between euthyroid and SCH groups, possibly due to small sample size.

Given the huge burden of type 2 diabetes in India, we can speculate the burden of undiagnosed TD in the society. The exact mechanism for such high association is not clear. Again, whether treating these patients with levothyroxine will reduce their metabolic complications are beyond the scope of this study. The future large-scale longitudinal study is likely to answer these questions.

Conclusion

This study reveals about one in four people living with diabetes are suffering from TD in this part of the country, which might warrant routine screening. A trend toward increased neuropathy and nephropathy was associated with rising TSH. This study also implies huge success of salt iodization program in this part of the country.

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Conflicts of interest

There are no conflicts of interest.

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