Original Article

Hypothyroidism in type 2 diabetic patients: a tertiary care hospital experience

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Abstract

Background *Hypothyroidism is one of the most common endocrine disorders encountered in endocrine practice worldwide which is more prevalent in elderly and women and its prevalence varies according to population studied. Both type 1 and type 2 Diabetic patients have higher prevalence of hypothyroidism than normal population not for direct etiology rather due to autoimmune association and increasing age. Co-existing hypothyroidism may impose co-morbid effects of dyslipidemia, atherosclerosis, hypertension and renal impairment on diabetic patients.*

Objective *This study was designed to find out frequency and association of clinical and sub-clinical hypothyroidism in adult type 2 diabetic subjects.*

Method *This was a cross sectional study conducted during the period of December 2009 to November 2010 in a tertiary care specialized hospital, (BIRDEM). Thyroid hormone (FT_4 and TSH) was studied among 227 adult type 2 diabetic subjects.*

Results *Among 227 study subjects, female respondents were 67%. Age (in years) was as mean± SD (SE) and (95% CI): 53.95±11.6 (.77) and (52.44-55.47). Thyroid hormone (FT4 and TSH) was assayed. FT4 (in pmol/L) of this population was as mean± SD (SE) and (95% CI): 13.05±2.66 (.18) and (12.71-13.4) and TSH was (in μIU/ml) as mean± SD(SE) and (95% CI): 4.12±7.03(.47) and (3.2-5.04). Sixty nine (30.4%) of them were hypothyroid and rest 158 (69.6%) were euthyroid. Among the hypothyroid cases, 17.6% were cases of sub-clinical hypothyroidism and 12.8% were of clinical hypothyroidism.*

Conclusion *Diabetic population have higher prevalence of hypothyroidism. While planning therapeutic approaches for diabetic patients, clinical and sub clinical hypothyroidism always should be taken into consideration. Diabetic patients with or without complication particularly with poor glycemic control, should be routinely screened for hypothyroidism.*

Key words: *Hypothyroidism, type 2 Diabetes mellitus, Euthyroid*

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Introduction

Hypothyroidism is one of the most common endocrine disorders encountered in endocrine practice worldwide. It is a clinical syndrome resulting from deficient production of thyroid hormones or a defect in thyroid receptor activity which may manifest from birth or be acquired, which in turn results in generalized slowing down of metabolic process. The condition is nearly 10 times more common in females than males and the incidence is also higher in the elderly, and in some racial and ethnic groups[1]. Prevalence of hypothyroidism varies depending on the population studied. In the Unites States 0.3% population have

overt hypothyroidism[2,3]. According to etiology, hypothyroidism can be divided into primary hypothyroidism and central hypothyroidism. Primary hypothyroidism is the etiology in majority of cases of hypothyroidism[1]. Common causes of primary hypothyroidism are iodine deficiency, chronic autoimmune thyroiditis (Hashimoto's thyroiditis), subacute thyroiditis, silent thyroidits, postpartum thyroiditis, iodine excess, thyroid surgery, I ^{131}therapy, external irradiation, infiltrative disorders, drugs, agenesis and dysgenesis of thyroid gland. Among these, iodine deficiency is the most common cause worldwide[4]. Chronic autoimmune thyroiditis (Hashimoto's) is the leading cause in iodine-sufficient area. This condition is several times more prevalent in women than men. Up to 15% of elderly women may have positive anti-thyroid autoantibodies[2]. Sub-clinical hypothyroidism (SCH) is the term used to define a state in which serum T4 and T3 levels are within normal limits, but there is underlying mild thyroid failure, as evidenced by a mild increase in serum TSH (4.5-10 μIU/ml)[5]. Overall prevalence of subclinical hypothyroidism ranges from 4% to as high as 10%[6]. The etiology of subclinical hypothyroidism (SCH) is similar to that of overt clinical hypothyroidism. In one study, approximately 55% of patients who had mild thyroid failure had chronic autoimmune thyroiditis [7]. There are potential risks that progression of SCH to overt hypothyroidism. Increased incidence of aortic atherosclerosis (odds ratio, 1.7) and myocardial infarction (odds ratio, 2.3) were revealed in women with subclinical hypothyroidism[8]. This condition is also consistently associated with elevation of total and low density cholesterol [9].

Diabetes mellitus is one of the most common non-communicable diseases globally. Number of people with diabetes was estimated to be 285 millions in the year 2010 and has been projected to rise to 438 million in the 2030 [10]. Estimated national prevalence of diabetes mellitus of Bangladesh is 6.1% for the year 2010[10]. Type 2 diabetes is by far the commonest form globally, accounting for more than 85% of cases. In Bangladesh, the crude prevalence of type 2 diabetes is 4.3% and IFG is 12.4%[11]. Diabetic patients have a higher prevalence of thyroid disease compared with normal population[12]. Among the thyroid diseases prevalent in diabetes, hypothyroidism (clinical and sub-clinical) is the commonest disorder. In addition to the autoimmune link between thyroid disease and type 1 diabetes, prevalence of thyroid diseases are also higher than normal in type 2 diabetes, with hypothyroidism being the most common disorder[12]. Hypothyroidism is not a direct etiology for development of diabetes mellitus but both are more commonly found in the elderly, contributing to a high association[13]. Hypothyroidism is commonly accompanied by hypertension, dyslipidemia including elevated total cholesterol, LDL cholesterol and triglyceride which increases the risk of cardiovascular diseases in diabetic patients. Recently ADA has recommended that TSH should be measured as a component of comprehensive diabetes evaluation in type 1 diabetes, diabetes with dyslipidemia or women over age of 50 years [14].

Whether in our population, hypothyroidism is more frequent and associated with type 2 diabetes has not also been well studied. Hence, this study was designed to find out frequency and association of clinical and sub-clinical hypothyroidism in adult type 2 diabetic patients.

Methods:

This cross sectional study was to determine the frequency and association of clinical and sub-clinical hypothyroidism in Type 2 diabetic patients. Sample was selected purposively from inpatient department of BIRDEM on the basis of availability according to following selection criteria: diagnosed cases of type 2 diabetic patients of both sex, age more than 18 years and patients not having co-morbid condition. Following diabetic patients were excluded from the study: age below 18 years, pregnant or lactating women with diabetes mellitus or GDM, type 2 diabetic patients with known history of thyroid diseases with or without treatment (medical, surgical, radio-iodine etc), patients receiving any medicine that may alter thyroid function, suffering from severe co-morbid conditions, type 1 diabetic patient, and patient with endocrine disorders other than diabetes and hypothyroidism were excluded. After initial screening, 227 adult diabetic patients (20 to 79 years) were selected in this study according to selection criteria. The purpose of the study was explained to each subject in detail. The data were collected in a pre-formed standard printed data

collection form after taking written informed consent of the patient. The study was conducted in full record with ethical principle.

After primary selection a detailed clinical history regarding age, sex, socioeconomic condition etc. was taken from the patient by interview. Every patient was examined thoroughly regarding height, weight, BMI. Standing height was measured using appropriate scales (detect-medic, detect scales INC, USA) with minimal clothes. Height was recorded to the nearest 5 mm. Weight was recorded to the nearest 0.5. BMI of the subjects were calculated using standard formula, BMI=Weight (kg) / Height (m2). Sitting BP was measured in both arms after at least 15 minutes of rest with an appropriate sphygmomanometer using phase-1 and phase-5 Korotkoff sounds. A second measurement was made at least after 3 minutes in the arms with the highest measurement. The mean of two measurements was used for systolic and diastolic blood pressure. Laboratory tests reports of Hb%, FPG, HBA1c%, fasting lipid profile, resting ECG, urine for protein, serum creatinine, CCR, 24 hour UTP, urine for microalbumin were collected. Available previous medical documents were also thoroughly reviewed.

Study subjects were then tested with FT4 and TSH to evaluate the status for hypothyroidism. Serum FT4, TSH measurement was made by Abbott AXSYM system device by using Microparticle Enzyme Immunoassay (MEIA) method. A high serum TSH level (4.5-10 μIU/ml) and a normal free thyroxine level was required for the diagnosis of SCH . A high TSH (>4.5μIU/ml) and low FT4 (<10.3 pmol/L) was required for diagnosis of clinical (primary) hypothyroidism (Surks et al 2004). All the data were checked and edited. Then data were entered into computer with the help of software SPSS for windows programmed version 15. After frequency run, data were cleaned and frequencies were checked. An analysis plan was developed keeping in view with the objectives of the study.

Results

Thyroid hormone (FT4 and TSH) was assayed for 227 diabetic subjects admitted in BIRDEM Hospital. FT4 (in pmol/L) of this population was as mean± SD (SE) and (95% CI): 13.05±2.66 (.18) and (12.71-13.4) and TSH (in μUl/ml) was as mean± SD(SE) and (95% CI): 4.12±7.03(.47) and (3.2-5.04). (Table-I)

Sixty nine (30.4%) of them were hypothyroid and rest 158 (69.6%) were euthyroid. Among the hypothyroid cases, forty (17.6%) of them were cases of sub-clinical hypothyroidism and rest (n=29, 12.8%,) were of clinical hypothyroidism. Hypothyroid cases had FT4 (in pmol/L) as mean± SD (SE) and (95% CI): 10.82±2.71 (.32) and (10.17-11.47) and TSH (uIU/ml) as mean± SD (SE) and (95% CI): 9.16±1.11 (1.34) and (6.47-11.84) and euthyroid subject had FT4 (in pmol/L) as mean± SD (SE) and (95% CI): 14.03±1.95 (.15) and (13.72-14.34) and TSH (uIU/ml) as mean± SD (SE) and (95% CI): 1.91±1.03 (.08) and (1.75-2.08). (Table I). Other variables of the study were - Age, BMI, SBP, DBP, Hb%, FBG, HbA1c%, serum creatinine, CCR, Serum total cholesterol, TG,, HDL and LDL. The results were as follows: (Table II)

Age (in years) as mean± SD (SE) and (95% CI): 53.95±11.6 (.77) and (52.44-55.47), BMI kg/m2 as mean± SD (SE) and (95% CI): 25.5±4.16 (.28) and (24.92-26.02), SBP mmHg as mean± SD (SE) and (95% CI): 129.14±17.25 (1.14) and (127.0-131.39), DBP mm Hg as mean± SD (SE) and (95% CI): 78.91±8.93 (.59) and (77.71-80.05), Hb in gm/dl as mean± SD (SE) and (95% CI): 11.20±1.5 (.1) and (11.0-11.4), FBG in mmol/l as mean± SD (SE) and (95% CI): 10.26±7.35 (.49) and (9.3-11.23), HbA1c % as mean± SD (SE) and (95% CI): 9.71±2.2 (.15) and (9.42-10.0), serum creatinine mg/dl as mean± SD (SE) and (95% CI): 1.36±.45 (.05) and (1.26-1.45), CCR ml/min as mean± SD (SE) and (95% CI): 66.8±34.4 (2.29) and (62.3-71.3), serum total cholesterol as mean± SD (SE) and (95% CI): 187.97±50.24 (3.33) and (181.4-194.54), TG in mg/dl as mean± SD (SE) and (95% CI): 212.22±124.86(8.28) and (195.40-228.55), HDL in mg/dl as mean± SD (SE) and (95% CI): 34.14±11.95 (.79) and (32.5-35.7), LDL in mg/dl as mean± SD (SE) and (95% CI): 100.9±36.71 (2.44) and (96.1-105.73).

Logistic analysis documented as a group Hypothyroid subjects (69) were different from the euthyroid subjects (158(sig. 0.000) when age , BMI, systolic BP, diastolic BP, Hb%, fasting blood glucose, HbA1c,FT4,TSH, CCR, Cholesterol, TG, HDL and LDL were considered as co-variates. Among the covariates only - FT4 and TSH had significant influence (sig. 0.000) on the grouping. (Table III)

Socio-demographic analysis showed, female respondents were 67% and rest were males (n= 75, 33%) and 99.1% were married. Among the total study subjects 30.8% completed their graduation. Only 9.3% % were found illiterate. Most of them were from upper and middle class socio-economic condition (42.7% and 45.5%).

Table I *Thyroid hormone (FT_4 and TSH) in diabetic subjects (n=227).*

Population	FT4 pmol/L As Mean ±SD(SE) (95% CI)	TSHμIU/ml As Mean ±SD(SE) (95% CI)
Diabetic Subject (N227)	13.05±2.66 (.18) (12.71-13.4)	4.12±7.03 (.47) (3.2-5.04)
DM Hypothyroid (69)	10.82±2.71 (.327) (10.17-11.47)	9.16±1.11 (1.34) (6.47-11.84)
DM Euthyriod (158)	14.03±1.95 (.15) (13.72-14.34)	1.91±1.03 (.08) (1.75-2.08)

NB: Among 227 diabetic subjects 69 had hypothyroidism and rests (158) were euthyroid.
DM= Diabetes Mellitus
$FT_{4=}$ serum free thyroxine
TSH= Thyroid Stimulating Hormone.

Table II *Clinical and biochemical characteristics of diabetic subjects (n=227).*

	Total population (n=227)	
	Mean±SD (SE)	95% CI
Age (years)	53.95±11.6(.77)	52.44-55.47
BMI kg/m^2	25.5±4.16(.28)	24.92-26.02
SBP(mmHg)	129.14±17.25(1.14)	127-131.39
DBP (mmHg)	78.91±8.93(.59)	77.71-80.05
Hb gm/dl	11.20±1.5(.1)	11-11.4
FPG (mmol/l)	10.26±7.35(.49)	9.3-11.23
HBA1c%	9.71±2.2(.15)	9.42-10.0
FT4(pmol/L)	13.05±2.66(.18)	12.71-13.40
TSH (μ IU/ml)	4.12±7.03(.47)	3.2-5.04
S. Creatinine(mg/dl)	1.36±.45(.05)	1.26-1.45
CCR ml/min	66.8±34.4(2.29)	62.3-71.3
T.Cholesterol (mg/dl)	187.97±50.24(3.33)	181.4-194.54
Triglyceride (mg/dl)	212.22±124.86(8.28)	195.40-228.55
HDL (mg/dl)	34.14±11.95(.79)	32.5-35.7
LDL(mg/dl)	100.9±36.71(2.44)	96.1-105.73

NB: Table shows clinical and biochemical variables of the study population in mean±SD(SE) and 95% CI.
SD= standard deviation, SE= standard error, CI= confidence interval

Table III

Logistic regression analysis between Hypothyroid subjects (69) and Euthyroid subjects (158)

A linear logistic regression analysis was done with thyroid status (hypothyroid vs euthyroid) of 227 diabetic cases as the dependent variable with 14 co-varieties (independent variable) namely age , BMI, systolic BP, diastolic BP, Hb, fasting blood glucose, HbA1c,FT4,TSH, CCR, Cholesterol, TG, HDL and LDL.

Coefficients(a)

Model		Unstandardized Coefficients		Standardized Coefficients	T	Sig.
		B	Std. Error	Beta		
1	(Constant)	2.060	.463		4.453	.000
	Age in years	-.002	.002	-.041	-.667	.506
	BMI of the respondents	.002	.006	.015	.261	.794
	Systolic BP	.002	.002	.077	1.093	.275
	Diastolic BP	.000	.004	-.009	-.128	.898
	Hb (gm/dl)	-.022	.018	-.072	-1.209	.228
	FBS (mmol/L)	.000	.003	-.002	-.039	.969
	Total Cholesterol	.000	.001	.021	.245	.807
	Triglyceride	.000	.000	.034	.531	.596
	HDL	.004	.002	.107	1.850	.066
	LDL	2.407E-05	.001	.002	.025	.980
	Hba1C%	.008	.013	.037	.606	.545
	S. Creatinine	-.003	.048	-.004	-.057	.954
	CCR	-.001	.001	-.072	-.884	.378
	FT4	-.074	.011	-.426	-6.662	.000
	TSH	.015	.004	.232	3.631	.000

a Dependent Variable: thyroid group.

NB: Logistic analysis documented that 69 Hypothyroid subjects are significantly different from the 158 euthyroid subjects (sig. 0.000) when 14 variables namely age , BMI, systolic BP, diastolic BP, Hb, fasting blood glucose, HbA1c,FT4,TSH, CCR, Cholesterol, TG, HDL and LDL considered as co-varieties. Among the covariates of only thyroid hormones (T4 and TSH) had significant influence (sig. 0.000) on the grouping.

Discussion

The prevalence of thyroid disease in patients with diabetes is significantly higher than that in the general population. In a reported study, the prevalence of hypothyroidism in diabetic patients was 4% [15]. An outpatient diabetes clinic in Scotland randomly screened 1,310 adult patients with diabetes for thyroid disease. The prevalence of thyroid disease was found to be 13.4%, of which 6.8% were diagnosed during the screening, with the highest in patients with type 1 diabetes (31.4%) and lowest in patients with type 2 diabetes (6.9%).The most common thyroid dysfunction was sub-clinical hypothyroidism (4.8%) followed by hypothyroidism (0.9%) [16]. A study conducted upon elderly (aged 65-92 years) population, prevalence of hypothyroidism was found to be 14% (9.7% in males and 18.2% in females) and that of DM was

11.5% (12.1% in males and 11.1% in females). In the study, 74% of the diabetics the diagnosis was made after the age of 60 years. Sub-clinical hypothyroidism was detected in 38% of all the hypothyroid subjects. The findings suggested that diabetes mellitus and primary hypothyroidism are common disorders in elderly subjects [17].

The association between Type 2 diabetes mellitus and sub-clinical hypothyroidism is well recognized, with the reported prevalence in diabetes varying from 2.2 to 17% [15, 18]. In a hospital based study, in type 2 diabetes mellitus who had abnormal TSH levels, subclinical hypothyroidism was most common (48.3%), followed by subclinical hyperthyroidism (24.2%), hypothyroidism (23.1%) [19]. In another study conducted upon 420 adult type 2 diabetic women, the prevalence of subclinical hypothyroidism was found to be 8·6%. Authors concluded that, in women with type 2 diabetes without known thyroid disease, subclinical hypothyroidism is a common but incidental finding and the routine screening of thyroid function in type 2 diabetes is questionable [20].

This was a hospital based cross sectional study carried out to find out frequency of clinical and sub-clinical hypothyroidism in type 2 diabetic patients. Clinical and sub-clinical hypothyroidism defined by assessing FT4 and TSH level. Among the study subject (n=227), 67% (n=152) were female and 33% (n=75) were male. The mean age of the study subjects in years was 53.95±11.6 SD(.77 SE) and 95% CI(52.44-55.47). In a report, mean age of type 2 diabetic patients who underwent thyroid function tests was 66.7 years which is higher than this study population [21].

In a study, overall hospital frequency of hypothyroidism was 10.3%, (clinical hypothyroidism 4% and SCH 6.3%) [21]. In this study, the hospital frequency of overall hypothyroidism among the type 2 diabetic patients was 30.4%% (n=69) with SCH 17.6% (n=40) and 12.8% (n=29) with clinical hypothyroidism which is higher than previous study. The Fremantle Diabetes Study found a 8.6% prevalence of SCH among women with type 2 diabetes [8].

In this study, hypothyroid cases had FT4(pmol/L): 10.82±2.71 (.32) and (10.17-11.47) and TSH(uIU/ml): 9.16±1.11 (1.34) and (6.47-11.84) and euthyroid subject had FT4(pmol/L): 14.03±1.95 (.15) and (13.72-14.34) and TSH(uIU/ml): 1.91±1.03 (.08) and (1.75-2.08). Mean TSH in euthyroid and in SCH subjects were 1.34(.41-3.99) and 5.61(4.03-12.50) respectively in the study conducted by Chen et al. [21]. Other study variables were- age, BMI, SBP, DBP,Hb%, FBG, HbA1c%, serum creatinine, CCR, serum total cholesterol, TG, HDL and LDL.

So this study concluded that hypothyroidism associated with it among type 2 diabetic patients the frequency of hypothyroidism among the total diabetic subjects was 30.4% with SCH 17.6% (n=40) and 12.8% (n=29) with clinical hypothyroidism. Logistic analysis documented that 69 Hypothyroid subjects were significantly different from the 158 euthyroid subjects (sig. 0.000) when 14 variables namely age , BMI, systolic BP, diastolic BP, Hb, fasting blood glucose, HbA1c,FT4,TSH, CCR, Cholesterol, TG, HDL and LDL considered as co-varietes. Among the covariates of only thyroid hormones (T4 and TSH) had significant influence (sig. 0.000) on the grouping.

References

1. Devdhar M, Yasser H, Kenneth D. Hypothyroidism. Endocrinol Metab Clin N Am 2007; 36: 595-615
2. Tunbridge WMG, Evered DC, Hall R, et al. The spectrum of thyroid disease in the community; the Whickham Survey. Clin Endocrinol 1977; 7: 481-493
3. Vanderpump MP, Turnbridge WM, French JM, et al. The incidence of thyroid disorders in the community: a twenty year follow-up of Whickham Survey. Clin Endocrinol (Oxf). 1995; 43: 55-68
4. Andersson M, Takkouche B, Egli I, et al. Current global iodine status and progress over the last decade towards the elimination of iodine deficiency. Bull World Health Organ 2005; 83: 518-525
5. Surks MI, Ortiz E, Daniels GH, Sawin CT et al. Subclinical thyroid disease, scientific review and guidelines for diagnosis and management. JAMA 2004; 291: 228-238
6. McDermott MT, Ridgeway EC. Subclinical hypothyroidism is mild thyroid failure and should be treated. J Clin Endocrinol Metab 2001; 86: 4585-4590

7. Hamburger JI, Meier DA, Szpunar WE. Factitious elevation of thyrotropin in euthyroid patients[letter]. N Eng J Med 1985;313:267-268

8. Hak AE, Pols HA, Visser TJ, et al. Subclinical hypothyroidism is an independent risk factor for atherosclerosis and myocardial infarction in elderly women-The Rotterdam Study. Ann Intern Med 2000;132:270-278

9. Danese MD, Ladenson PW, Meinert CL, et al. Effect of thyroxin therapy on serum lipoproteins in patients with mild thyroid failure: a quantitative review of the literature. J Clin Endocrinol Metab 2000;85:2993-3001

10. IDF Diabetes Atlas 4th ed. International Diabetes Fedaration 2009

11. Sayeed MA, Mahtab H, Khanam PA, Latif ZA, Ali SM, Banu A, Ahren B, Azad Khan AK. Diabetes and impaired fasting glycemia In a rural population of Bangladesh. Diabetes Care 2003; 26(4):1034-1039

12. Wu P. Thyroid disease and diabetes. Clinical Diabetes 2000;18:38-39

13. Ober K. Polyendocrine syndromes. In: Leahy J, Clark N, Cafalu W, Eds. Medical management of diabetes mellitus. Marcel Dekker, Inc New York 2000:699–717

14. American Diabetes Association. Standard of medical care in diabetes-2010. Diabetes Care 2010;33 (1):S11–S61

15. Feely J, Isles TE. Screen for thyroid function in diabetics. Br Med J 1979;285:1678

16. Perros P, McCrimmon R, Shaw G, Frier B. Frequency of thyroid dysfunction in diabetic patients: value of annual screening.Diabet Med 1995;7:622–627

17. Flatau E, Trougouboff P, Kaufman N, Reichman N, Luboshitzky R. Prevalence of hypothyroidism and diabetes mellitus in elderly kibbutz members. Eur J Epidemiol. 2000;16(1):43-46

18. Smithson MJ. Screen for thyroid dysfunction in community population of diabetic patients. Diabet Med 1998;15:148–150

19. Celani MF, Bonati ME, Stucci N. Prevalence of abnormal thyrotropin concentrations measured by a sensitive assay in patients with type 2 diabetes mellitus. Diabetes Res 1994.;27(1):15-25

20. Chubb 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;62:480–486

21. Chen HS, Wu TE, Jap TS, Lu RA, Wang ML, Chen RL, Lin HD. Subclinical hypothyroidism is a risk factor for nephropathy and cardiovascular diseases in type 2 diabetes patients. Diabet Med 2007; 24(12):1336-1344