

PREVALENCE OF HYPOTHYROIDISM WITH MICROVASCULAR COMPLICATIONS IN TYPE 2 DIABETES MELLITUS

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ARTICLE INFO

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Key words: Type 2 Diabetes Mellitus, Hypothyroidism, Subclinical Hypothyroidism, Overt Hypothyroidism, Diabetic Retinopathy, Diabetic Nephropathy, Diabetic Neuropathy.



DOI: <http://dx.doi.org/10.15520/ijmhs.2016.vol6.iss6.142>

ABSTRACT

DM and Hypothyroidism are the two most common endocrine disorders in clinical practice. Also, diabetic patients have a higher prevalence of thyroid disorders compared to normal population. An unrecognized hypothyroidism may adversely affect the metabolic control and hence aggravate the complications of DM. So, it is essential to detect and treat the associated hypothyroidism before overt clinical manifestations. This study was done to compare the prevalence of microvascular complications of DM in euthyroid diabetic patients and diabetic patients with Hypothyroidism. 100 diabetic patients, without known hypothyroidism were screened for hypothyroidism and diabetic microvascular complications. Patients were investigated for RBS, FBS, HbA1c, FTP, RFT, USG Abdomen, Microalbuminuria, FLP and NCS. Diagnosis of DM was done following ADA 2014 guidelines. Hypothyroidism was classified as clinical and subclinical hypothyroidism. Prevalence of hypothyroidism was higher in diabetic patients, especially females. Subclinical hypothyroidism was detected in 21% and Overt Hypothyroidism in 12% of diabetic patients. Diabetic patients with hypothyroidism were found to have higher prevalence of diabetic microvascular complications compared to Euthyroid diabetics. This warrants screening of diabetic patients for thyroid functions. Failure to recognise the presence of abnormal thyroid hormone levels may be one of the reasons for poor outcomes in DM management.

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INTRODUCTION

Patients with Type 2 Diabetes mellitus (DM) have a higher prevalence of thyroid disorders compared with the normal population and the most common amongst them is SCH (Subclinical Hypothyroidism)^(1,2). Diabetic Retinopathy (DR) is one of the most common microvascular complications of DM and is the leading cause of blindness worldwide. Common risk factors for the development of microvascular complications include duration of diabetes, poor glycemic control, elevated blood pressure and dyslipidaemia.^(18,19) Diabetic Neuropathy occurs in about 50% of individuals with type 2 DM. It may manifest as polyneuropathy, mononeuropathy and / or autonomic neuropathy. As with other complications of DM, the development of neuropathy correlates with the duration of diabetes and glycaemic control. Diabetic nephropathy is the leading cause of End Stage Renal Disease (ESRD) and a leading cause of DM- related morbidity and mortality. Both micro- and macroalbuminuria in individuals with DM are associated with increased risk of cardiovascular risk. Like other microvascular complications, the pathogenesis of diabetic nephropathy is related to chronic hyperglycaemia. About 20% to 40% of patients with diabetes develop Diabetic Nephropathy.⁽⁴⁾ Hypothyroidism can be classified as overt and subclinical hypothyroidism. Overt

hypothyroidism (OH) is the symptomatic state of thyroid dysfunction with low serum thyroxin levels and elevated serum TSH (> 10 mU/L).⁽³⁾ Subclinical hypothyroidism (SCH) is defined as an asymptomatic state characterised by a normal serum thyroxin level and elevated serum concentration of thyrotropin (thyroid-stimulating hormone [TSH]) (5-10 mU/L).⁽³⁾ An unrecognized Hypothyroidism aggravates the microvascular complications of DM by altering intrinsic metabolic pathways. Despite this, there is a distinct lack of relevant research into risk factors associated with microvascular complications in type 2 DM with SCH and clinical hypothyroidism.

OBJECTIVE OF THE STUDY

To compare the prevalence of microvascular complications of Type 2 Diabetes Mellitus in euthyroid diabetic patients and diabetic patients with Hypothyroidism.

METHODOLOGY

The study was conducted out in SSIMS & RC, Davangere over a period of 12 months from January 2015 to December 2015 and was a cross- sectional study. One hundred patients with diabetes mellitus, without known Thyroid Dysfunction, were screened for Hypothyroidism and diabetic microvascular complications (Retinopathy,

Nephropathy, Neuropathy). Patients with infections, trauma, preexisting liver, renal or thyroid disease, patients on medication that alter thyroid functioning (drugs causing hypothyroidism), & pregnant women were excluded from the study..

Approval from the Institutional Ethics Committee Review Board was obtained. A detailed history taking and clinical examination was done including fundoscopy, MNSI.

Patient was investigated for RBS, FBS, PPBS, HbA1c, Fasting thyroid profile (fT3, fT4, TSH) by Chemiluminescent assay, blood urea, serum creatinine, Microalbuminuria by Immunoturbidometry, USG Abdomen, FLP (total cholesterol, low density cholesterol, high density cholesterol, triglycerides), nerve conduction studies (NCS). As lower extremity nerves are probably involved more, we designed our NCS accordingly. Bilateral peroneal and tibial nerves compound muscle action potential (CMAP) and sural nerves sensory nerve action potential (SNAP), nerve conduction velocity (NCV), amplitude, and distal latency were found out to detect diabetic neuropathy.

Diagnosis of DM was done based on symptoms of diabetes plus random blood glucose concentration >200 mg/dL or Fasting plasma glucose >126 mg/dL or HbA1C >6.5%.

Hypothyroidism was classified as clinical and subclinical hypothyroidism. Clinical Hypothyroidism being the symptomatic state of Thyroid Dysfunction with low serum thyroxine levels and elevated serum TSH (>10 mU/L). Subclinical hypothyroidism (SCH) was defined as an asymptomatic state characterized by a normal serum thyroxine level and elevated serum concentration of thyrotropin (thyroid-stimulating hormone [TSH]) (5-10 mU/L).

STATISTICAL METHODS APPLIED

The data was analysed using Epiinfo statistical software version 6.0. The categorical data was expressed in terms of percentage and ratios and comparison was done using either Chi-square test or Fisher’s exact test. The continuous data was expressed as mean ± standard deviation (SD) and comparison was done using Analysis of Variance test (ANOVA test). A probability value (‘p’ value) of ≤ 0.05 at 95% CI was considered as statistically significant.

RESULTS

The present one year hospital based cross-sectional study was done in the Department of General Medicine, S S Institute of Medical Sciences and Research Centre, Davangere, Karnataka. A total of 100 patients with type 2 diabetes mellitus were enrolled and all underwent screening for Hypothyroidism and diabetic microvascular complications

The salient findings of the study are as below:

Most of the patients (59 %) were males and male/female ratio was 1.44 : 1. The commonest age group was between 51- 60 years (38%), and the mean age was 62.42 +/- 11.31 years. Female diabetic patients had higher prevalence of Hypothyroidism (SCH= 76.2%, OH= 66.7%), with p value <0.001.

Table-1: Gender distribution of Hypothyroidism

	Gender		p-value
	Male	Female	
Euthyroidism	50 (74.6%)	17 (25.4%)	0.000
Sub-clinical hypothyroidism	5 (23.8%)	16 (76.2%)	
Overt hypothyroidism	4 (33.3%)	8 (66.7%)	

Table 1 shows increased prevalence of Hypothyroidism in female patients with Diabetes Mellitus compared to male patients.

Biochemical profile

Mean HbA_{1c} levels in euthyroid diabetic patients was 8.8 ± 2.1. Mean HbA_{1c} levels in diabetic patients with SCH was 9.0 ± 1.7. Mean HbA_{1c} levels in diabetic patients with overt hypothyroidism was 9.6 ± 2.1.

Mean serum TSH levels in euthyroid diabetic patients was 2.7 ± 1.3. Mean serum TSH levels in diabetic patients with SCH was 8.4 ± 1.4. Mean serum TSH levels in diabetic patients with overt hypothyroidism was 12.4 ± 1.3.

Diabetic Microvascular complications and Hypothyroidism profile

Prevalence of Diabetic Retinopathy was significantly higher in diabetic patients with Hypothyroidism with p value of 0.000. In Euthyroid diabetics, it was observed to be 13.4%, in Sub-clinical hypothyroid diabetics, it was observed to be 42.9% and in Overt hypothyroid diabetics, it was 66.7%.

Prevalence of Diabetic Nephropathy was significantly higher in diabetic patients with Hypothyroidism , with p value of 0.001. In Euthyroid diabetics, it was observed to be 9.0%, in Sub-clinical hypothyroid diabetics, it was observed to be 38.1% and in Overt hypothyroid diabetics, it was 41.7%.

Prevalence of Diabetic Neuropathy was significantly higher in diabetic patients with Hypothyroidism , with p value of 0.031. In Euthyroid diabetics, it was observed to be 16.4%, in Sub-clinical hypothyroid diabetics, it was observed to be 28.6% and in Overt hypothyroid diabetics, it was 50.0%.

Table-2: Overall prevalence of microvascular complications

Microvascular complication	Prevalence
Retinopathy	26%
Nephropathy	19%
Neuropathy	23%

Table-2 shows overall prevalence of microvascular complications in group of Diabetic Mellitus patients under the study. Diabetic Retinopathy was detected in 26%, Diabetic Nephropathy in 19% and Diabetic Neuropathy in 23% of the study population.

Prevalence of Hypothyroidism is higher in diabetic patients, especially females. In Euthyroid diabetics, it was observed to be 25.4%, in Sub-clinical hypothyroid diabetics, it was observed to be 76.2% and in Overt hypothyroid diabetics, it was 66.7%. Furthermore, diabetic patients with Hypothyroidism have higher prevalence of diabetic microvascular complications (Diabetic Retinopathy and Diabetic Nephropathy) and dyslipidaemia (raised total and LDL cholesterol and Triglycerides), compared to Euthyroid Diabetic patients.

Table-3: Prevalence of Microvascular complications in Hypothyroidism

Thyroid status	Microvascular complications		
	Retinopathy	Nephropathy	Neuropathy
Euthyroidism (67)	9 (13.4%)	6 (9.0%)	11 (16.4%)
Sub-clinical hypothyroidism (21)	9 (42.9%)	8 (38.1%)	6 (28.6%)
Overt hypothyroidism (12)	8 (66.7%)	5 (41.7%)	6 (50.0%)

Table-3 shows that there is an increased prevalence of microvascular complications in patients with Hypothyroidism compared to Euthyroid diabetics.

DISCUSSION

Diabetes mellitus and Thyroid Dysfunction

Thyroid hormones may influence glucose control through a variety of actions on intermediary metabolism. In patients with diabetes, hypothyroidism may influence metabolic control through effects on glucose metabolism, which include reductions in hepatic glucose output, gluconeogenesis and peripheral glucose utilization. The net effect of these processes is a predisposition to hypoglycaemia.⁽⁵⁾ Co-existent diabetes may also affect the efficacy of thyroid hormone treatment in patients with hypothyroidism.⁽¹⁷⁾

Surjeet Singh 2011 reported prevalence of hypothyroidism in 23.5% (15% subclinical and 8.75% overt hypothyroidism) and hyperthyroidism in 6.25% among 80 type 2 diabetes patients studied.¹⁰⁹ Laloo Demitrost 2012 reported 27.7% prevalence of hypothyroidism (16.3% subclinical and 11.4% overt hypothyroidism) and 3.5% prevalence of hyperthyroidism in 202 type 2 diabetes patients from Manipur.⁽⁷⁾ Radaideh et al in their study Thyroid Dysfunction in patients with type 2 diabetes mellitus in Jordan reported prevalence of 12.5% thyroid disease in type 2 diabetes patients.⁽⁸⁾ Athanasia papazafropoulou et al in their study prevalence of Thyroid Dysfunction among Greek type 2 diabetic patients attending 97 outpatient clinic reported 12.3% prevalence of Thyroid Dysfunction type 2 diabetes.⁽⁹⁾ Ghazali et al in their study Thyroid Dysfunction in type 2 diabetics seen at the university college hospital Ibadan, Nigeria had reported Thyroid Dysfunction in 29.7% of type 2 diabetics.

Results from our study are consistent with previously published reports from India, prevalence of subclinical hypothyroidism being 22% and prevalence of overt hypothyroidism being 12%.

Diabetic Microvascular complications and Thyroid Dysfunction

Vascular endothelial dysfunction is believed to be an important factor in the pathogenesis of microvascular and macrovascular complications in diabetes. Endothelial dysfunction in Type 2 DM occurs as a result of hyperglycemia, growth factors, vasoactive agents and components of metabolic syndrome.¹¹³ Endothelial dysfunction has also been reported in subclinical hypothyroidism as well as in those with upper normal TSH values.⁽¹⁰⁻¹³⁾

The association between microvascular complications and Thyroid Dysfunction has not been extensively investigated. Among the few studies done on the subject, the findings have been contradictory.

Chen et al reported an association between subclinical hypothyroidism and nephropathy but no association with retinopathy was found.⁽¹⁴⁾ Article by Wright DL, Shah JH: Diabetic neuropathic cachexia and hypothyroidism shows positive association of diabetic neuropathy with Thyroid Dysfunction. Yasuda et al, found an association between subclinical hypothyroidism and albuminuria⁽¹⁶⁾. Yang et al, on the other hand, reported an association between retinopathy and subclinical hypothyroidism and with those with TSH values in the high upper normal range (2.0-4.0 μ IU/ml)⁽¹⁵⁾. Kim et al reported an association between subclinical hypothyroidism and retinopathy but no association with nephropathy.⁶ Study

done by Furukawa S et al showed that the SCH group had a higher prevalence of dyslipidemia ($p= 0.008$) and diabetic nephropathy ($p = 0.014$) than the euthyroid group.

In the present study, prevalence of diabetic retinopathy was significantly higher in diabetic patients with Hypothyroidism (SCH= 42.9%), (OH= 66.7%), compared to euthyroid diabetic patients (13.4%). Prevalence of diabetic nephropathy was significantly higher in diabetic patients with Hypothyroidism (SCH= 38.1 %), (OH=41.7%), compared to euthyroid diabetic patients (9.0%). Prevalence of diabetic nephropathy was significantly higher in diabetic patients with Hypothyroidism (SCH= 28.6 %), (OH=50%), compared to euthyroid diabetic patients (16.4%). There was increased prevalence of dyslipidaemia in diabetic patients with Hypothyroidism in the form of borderline elevation of total cholesterol levels and LDL cholesterol levels.

The prevalence of diabetes and thyroid diseases appears to be very high in India. India already has huge burden of diabetes and approximately 65.1 million diabetes patients as reported by international diabetes federation 2013. Prevalence of hypothyroidism is also increasing in India the latest report by Unnikrishnan AG 2013 suggests prevalence of hypothyroidism as high as 10.95% among adults.⁽⁹⁾

Moreover prevalence of Hypothyroidism is high among Type 2 Diabetes mellitus patients, and prevalence of microvascular complications of diabetes mellitus is more common in diabetic patients with Hypothyroidism, probably due to worsening of the insulin resistance by the co-existing Hypothyroidism.

Limitation of the present study was that it was observational in nature. Therefore a controlled study would be more appropriate to confirm the association of Hypothyroidism and microvascular complications. Moreover, the screening tests for microvascular complications were done only once, ideally which should have been repeated for confirmation.

CONCLUSION

Prevalence of Hypothyroidism is high among Type 2 Diabetes mellitus patients especially females. From the findings of the study it may be concluded that the prevalence of microvascular complications of diabetes mellitus and dyslipidaemia is more common in diabetic patients with Hypothyroidism. Failure to recognise the presence of abnormal thyroid hormone levels may be one of the reasons for poor outcome of diabetes mellitus management. Hence, this warrants screening of diabetic patients for thyroid functions.

Abbreviations: SCH-Hypothyroidism, OH- Overt Hypothyroidism

Statement of competing interests: The authors have no competing interests.

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