

ASSOCIATION OF HYPOTHYROIDISM WITH MICROVASCULAR COMPLICATIONS AMONG PATIENTS OF TYPE-2 DIABETES MELLITUS

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Article Info: Received 14 October 2021; Accepted 26 November 2021

DOI: <https://doi.org/10.32553/ijmbs.v5i12.2341>

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Conflict of interest: No conflict of interest.

Abstract

Introduction: Diabetes mellitus (DM) is common metabolic disorder leading to various complications including microvascular complication. Diabetes and thyroid dysfunction can result in abnormalities of one another, as both are strongly implicated in cellular metabolism. Aim of study was to establish any association between hypothyroidism and micro-vascular complications in patients of type 2 DM.

Material and Methods: This Hospital based Cross sectional analytical Study was included 80 Euthyroid and 80 hypothyroid patients of type 2 DM. These patients were subjected to fundus examination (for retinopathy), urine for spot albumin and creatinine ratio and routine microscopy (for nephropathy), clinical examination and NCV (for neuropathy).

Results: Age of patients ranged from 30 – 80 years. Most patients had duration of Diabetes > 5 years. Diabetic retinopathy was found in 15% Euthyroid and 37.5% Hypothyroid diabetics ($p=0.002$). Neuropathy was more in Hypothyroid (35%) as compared to Euthyroid (12.5%) patients ($p=0.003$). Prevalence of Nephropathy was also significantly more ($p=0.011$) in Hypothyroids (60%) as compared to Euthyroid (38.75%).

Conclusion: Significant association was found between hypothyroidism and micro vascular complications in type 2 Diabetes mellitus. Screening of diabetics for thyroid functions is essential to reduce morbidity.

Keywords: Diabetes, thyroid, retinopathy, neuropathy, nephropathy

Introduction

Diabetes mellitus (DM) is common metabolic disorder characterized by hyperglycemia resulting from defective insulin action, insulin secretion or both.¹ Diabetes mellitus is the most widespread endocrine disorder upsetting the developing population. The occurrence for all age group estimated around 2.8% in 2000, and is likely to amplify to 4.4% by 2030.² Diabetes is known to slowly lead to various complications including microvascular complication. Diabetic Retinopathy is one of the most frequent microvascular complications of DM and is the foremost cause of blindness throughout the world.^{3,4} Around 20% - 40% of patients having diabetes develop Diabetic Nephropathy.⁵ Diabetic nephropathy is the foremost reason of End Stage Renal Disease and a leading reason of DM associated morbidity and mortality. Diabetic Neuropathy occurring in around 50% of individuals with DM can manifest as poly/mono and/or automatic neuropathy.⁶

Established risk factors for the development of microvascular complications include duration of diabetes, poor glycemic control, prominent blood pressure and dyslipidaemia.⁷ Diabetes and thyroid are two common endocrine disorders seen within population of adults. Insulin deficit and excess / deficit of thyroid hormones can be resulted in purposeful abnormalities of one another, as both are strongly implicated in cellular metabolism. Type 2 Diabetes mellitus patients have elevated occurrence of

thyroid disorders in comparison to the normal population and the most frequent among them is Subclinical Hypothyroidism.

Glycemic control is also described to be affected by Thyroid hormones through a variety of actions over intermediary metabolism. Hyperglycemia is promoted by surplus thyroid hormone levels in the course to ease glucose intestinal assimilation enhancing glycolysis and gluconeogenesis and escalating insulin authorization.⁸⁻¹¹ Only few studies have reported an amplified occurrence of nephropathy and retinopathy in type 2 diabetic patients with hypothyroidism compared to euthyroid, while some have refuted it.¹²⁻¹³

Hence present study was conducted with the aim to establish any association between hypothyroidism and micro vascular complications in patients of type 2 diabetes mellitus.

Material and Methods:

This Hospital based Cross sectional observational Study was conducted at Department of Medicine at one of the largest tertiary care centre of Northern India, from June 2018 to May 2019. This study included 80 Euthyroid and 80 Hypothyroid patients of type 2 diabetes mellitus, aged >25 years, of either gender were recruited from OPD and

IPD of Department of Medicine. These patients were subjected to various tests like thyroid functions, lipid profile, HbA1c, fundus examination (for retinopathy), urine for spot albumin and creatinine ratio and routine microscopy (for nephropathy), clinical examination and NCV (for neuropathy). All laboratory tests were done at the central lab of the centre under similar conditions using same standard technique.

Based on the thyroid profile the patients were divided and recruited consecutively till sample size was achieved for both groups. Pregnant females, Patients with infections & preexisting kidney and liver diseases, Patients with hypertension and on nephrotoxic drugs, Patient on medication that alter thyroid function other than levothyroxine were excluded from the study. Sample was calculated at 95% confidence and 80% power to verify an expected difference of 20.36% cases with neuropathy in Hypothyroid and Euthyroid (36.36% v/s 16.4%).

Ethical clearance was obtained from Institutional Ethics Committee prior to initiation of study. Written informed consent was obtained from all patients prior to inclusion into the study.

Statistical analysis: Continuous data were summarized as mean and standard deviation, and difference in means was analyzed using student's 't' test. Categorical variables were summarized as frequency and proportion and difference in

proportion was analyzed using chi square test. A p value ≤ 0.05 was taken as statistically significant. All statistical analysis was done using Epi info version 7.2.1.0 statistical software.

Results:

A total of 160 Type 2 diabetics were included in the study with age ranging from 30 – 80 years. Males were slightly more than females. Most patients had duration of Diabetes > 5 years. Both groups were similar in relation to their baseline characteristics (Table 1).

Mean TSH was significantly raised in Hypothyroids, while T3 and T4 levels were significantly less among hypothyroids. No significant difference was seen in Lipid profile among the two groups. Mean ACR was more in hypothyroids, but the difference was not statistically significant (Table 2).

On fundus examination diabetic retinopathy (both proliferative / non proliferative) was found in 15% Euthyroid and 37.5% Hypothyroid diabetics ($p=0.002$). Similarly neuropathy was more in Hypothyroid (35%) as compared to Euthyroid (12.5%) patients ($p=0.003$). Prevalence of Nephropathy was also significantly more ($p=0.011$) in Hypothyroids (60%) as compared to Euthyroid (38.75%).

Table 1: Baseline characteristics of study subjects

		Euthyroid	Hypothyroid	P value
Age (years)		50.05 ± 12.71	49.71 ± 11.78	0.777
Gender	Female	32 (40%)	37 (46.25%)	0.523
	Male	48 (60%)	43 (53.75%)	
Duration of DM (years)		6.34 ± 3.48	6.26 ± 3.60	0.634
HbA1c level (%)		8.54 ± 2.33	8.49 ± 2.12	0.544

Table 2: Frequency of microvascular complications among study subjects

	Euthyroid	Hypothyroid	P value
TSH (mU/L)	2.34 ± 1.35	8.75 ± 4.68	< 0.001 (S)
T3 (mcg/dl)	2.82 0.36	1.68 0.53	< 0.001 (S)
T4 (mcg/dl)	0.94 0.197	0.73 0.29	< 0.001 (S)
Total cholesterol (mg/dl)	150.5 38.38	152.8 35.04	0.688
Triglyceride level (mg/dl)	157.4 113.7	147.8 41.44	0.479
HDL level (mg/dl)	43.33 11.5	46.5 14.78	0.132
LDL level (mg/dl)	96.61 28.32	101.6 23.34	0.238
ACR	39.59 45.62	53.4 55.94	0.089

Table 3: Frequency of microvascular complications among study subjects

	Euthyroid	Hypothyroid	P value
Retinopathy	12 (15%)	30 (37.5%)	0.002 (S)
Neuropathy	10 (12.5%)	28 (35%)	0.003 (S)
Nephropathy	31 (38.75%)	48 (60%)	0.011 (S)

Discussion:

Poor glycemic control and duration of diabetes are known risk factors for development of micro vascular complications. Thyroid disorders are documented to be more common among diabetics and they in turn are thought to increase risk of complication.

A total of 160 patients were enrolled in the study. Of these, 69 (43.13%) were females and 91(56.88%) were males. Past studies have also reported diabetes to be more in males.^{14,15} The mean age of euthyroid patients in our study population was 50.05 years and that of hypothyroid patients was 49.71 years. Prevalence of diabetes is known increase with age and similar finding have been reported by other studies.^{14,16,17} The mean duration of diabetes in our study population was 6.34 years for euthyroid and 6.26 years for hypothyroid patients. The mean HbA1c (%) of our study population ranged from 5.2 to 17% and median of 7.84%, which is comparable to studies done earlier.^{16,18}

The mean value of TSH (μ IU/ml) in our study population was 8.75 ± 4.68 in hypothyroid and 2.34 ± 1.35 in euthyroid patients. The mean TSH have been reported to be around 7 – 8 μ IU/ml, in hypothyroid population.^{14,19}

In our study, Retinopathy was seen more in Hypothyroid diabetics (37.50%), as compared to Euthyroid diabetics (15%). Diabetic retinopathy is more frequently seen in older individuals and those with longer interval of diabetes. In a study conducted by Usha Humbai et al²⁰ (2016), diabetic retinopathy was considerably higher ($p=0.001$) in diabetic patients with overt hypothyroid diabetics (66.7%) and subclinical hypothyroidism (42.9%) as compared to euthyroid diabetics (13.4%). In a meta-analysis done, the pooled effect anticipated from eight included studies demonstrated that hypothyroidism can increase the diabetic retinopathy risk by 2.13 times ($p < 0.001$).

In present study nephropathy was significantly more ($p=0.011$) in hypothyroid (60.00%) as compared to euthyroid patients (38.75%). A similar study observed that serum TSH levels were linked with diabetic nephropathy, but not with diabetic retinopathy.¹⁴ The multivariate analysis established the higher incidence of diabetic kidney disease with higher TSH levels. Thyroid function was an independent factor for diabetic nephropathy in subjects with type 2 diabetes mellitus. Shinya Furukawa et al²¹ in Japan (2014) described a appreciably higher occurrence of diabetic nephropathy in the hypothyroid patients compared to the euthyroid group ($p = 0.008$). GFR in subclinical hypothyroid group was subordinate than in the euthyroid group ($p=0.031$).

Contrary to this, study conducted by Feng Gao et al²² (2014), no relationship could be recognized between hypothyroidism and nephropathy. This contradiction could be due to bias in selection of patients.

In present study diabetic neuropathy was significantly ($p=0.003$) more common in hypothyroids (35.00%) as compared to euthyroids (12.50%). Similar to this, in an Indian study by Usha Humbai et al²⁰ (2016), diabetic neuropathy was considerably higher ($p = 0.0031$) in evident hypothyroid diabetics (50%) and subclinical hypothyroid diabetics (28.6%) as compared to euthyroid diabetics (16.4%).

Several mechanisms may be implicated in the relationship between thyroid dysfunction and microvascular complications in diabetes. Firstly, it has been established that insulin resistance is linked with clinical and subclinical hypothyroidism. A correlation between insulin resistance and micro albuminuria has been reported. A possible mechanism could be defective fibrinolysis or impaired vasodilatation linked with insulin resistance and hypothyroidism, decreased paraoxonase and aryl esterase activities, sense that the anti-oxidative ability in hypothyroidism decreased appreciably. Subclinical hypothyroidism is frequently complicated with endothelial dysfunction, manifest by thickening of the capillary basement membrane. It has been reported that endothelial dysfunction can influence the pathogenesis of diabetic complications. Thyroid hormone directly influences kidney growth, kidney structure, and many of its functions. Hypothyroidism affects kidney function indirectly through cardiac dysfunction, peripheral vascular resistance, endothelial dysfunction, and renal hemodynamic.^{14,20,21}

Limitation of study: Study was conducted at a tertiary care hospital where patients with complications are more likely to present, and a risk of Berksonian bias can be a possibility.

Conclusion:

Significant association was found between hypothyroidism and micro vascular complications (retinopathy, nephropathy and neuropathy) in type 2 Diabetes mellitus. Failure to distinguish the occurrence of abnormal thyroid hormone levels might be one of the reasons for poor outcome of diabetes mellitus management, hence screening of diabetic patients for thyroid functions is essential for timely management to reduce morbidity and early mortality in type 2 diabetic patients.

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