OBSERVATIONAL STUDY EVALUATING ASSOCIATION OF TYPE 2 DIABETES MELLITUS AND THYROID DYSFUNCTION

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ABSTRACT

BACKGROUND

Type 2 diabetes mellitus (T2DM) appears to influence thyroid function by various mechanisms. The exact association between T2DM and thyroid dysfunction has not been documented from Kerala; hence this study is conducted to determine the prevalence of thyroid dysfunction among T2DM patients and to determine the association between T2DM and thyroid dysfunction.

MATERIALS AND METHODS

Our prospective observational study enrolled 150 T2DM patients diagnosed using ADA diagnostic criteria. Institutional Ethics Committee approved the study and written informed consent was obtained from all study participants. Data was collected in case record forms, which included history, examination findings and laboratory investigations assessing glycaemic control and thyroid function. Values are expressed as mean (standard deviation). Analysis was done using R® and tests of significance used were independent sample 't' test, ANOVA and Chi square test. $p < 0.05$ was considered statistically significant.

RESULTS

Mean age, duration of T2DM and glycated haemoglobin (HbA1c) of the study participants were 60.1 (7.9) years, 13 (5.9) years and 7.7 (0.8)% respectively 56.7% participants were having higher than normal Body Mass Index (BMI). 80% of participants were females and thyroid dysfunction was seen in 16.7% participants. Among the study participants, 13.3% (n=20) had overt hypothyroidism, 2% (n=3) had subclinical hypothyroidism and 1.3% (n=2) had overt hyperthyroidism. Significant difference in weight ($p=0.01$), BMI ($p<0.001$) and HbA1c ($p=0.006$) was observed when participants were categorized based on thyroid swelling. Significant difference in BMI ($p<0.001$) and fasting plasma glucose ($p<0.001$) was observed when participants were categorized based on type of thyroid dysfunction. Significant difference in thyroid stimulating hormone ($p<0.001$) and HbA1c ($p=0.02$) was observed when participants were categorized according to BMI. Association was observed between ADA glycaemic goal and type of thyroid dysfunction ($p<0.001$).

CONCLUSION

16.7% of the T2DM patients had thyroid dysfunction, hypothyroidism was the predominant dysfunction. Failure to recognize the presence of thyroid dysfunction among T2DM patients may be a primary reason for poor management of diabetes. We recommend screening for thyroid dysfunction and regular monitoring of thyroid function in T2DM patients.

KEYWORDS

Type 2 Diabetes Mellitus, Hypothyroidism, Hyperthyroidism.

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BACKGROUND

Diabetes mellitus (DM) is a chronic endocrine disorder characterized by hyperglycaemia due to reduced insulin secretion or reduced response of tissues to insulin or both.[1]The global prevalence and the complications associated with this pandemic is on the rise, with India housing the second largest population of diabetics[2] of which the major proportion is type 2 diabetes.[3] The Indian prevalence of type 2 diabetes mellitus (T2DM) ranges between 5-17%[2] with higher prevalence from southern states. The possible reasons for the dramatic rise in burden of this disorder are sedentarism, fast food culture, ageing population and urbanization. DM invariably affects the quality of life by increasing the mortality and mortality and by imposing a financial burden on the family. Global

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prevalence of thyroid disorders ranges between 2-6.4%, with higher prevalence among elderly[4] and the prevalence in India ranges between 10.9-12.5%.[5,6] The prevalence of thyroid disorders in diabetic patients varies from 12-31%,[7,8] with highest prevalence among female diabetics. Thyroid dysfunction in diabetic patients has been mesmerizing the scientific community since 1920s. The first reported association was between hyperthyroidism and worsening of glycemic control,[9] followed by reports of improvement of glycemic control with surgical removal of thyroid. The association of hypothyroidism and T2DM has been documented,[9] the widely accepted pathogenesis being autoimmune mechanisms causing destruction of pancreatic β cells.[10]Thyroid hormones exert a control over insulin secretion, hypothyroid states reduce insulin secretion and hyperthyroid states increase the insulin secretion and increase the metabolism of insulin.[11,12]Though these mechanisms have been postulated the exact association of thyroid disorders and T2DM and the prevalence of thyroid dysfunction among T2DM patients in our setting have not been clearly evaluated, hence this study.

MATERIALS AND METHODS

The present prospective observational study enrolled 150 T2DM patients attending outpatient of Department of General Medicine, Sree Gokulam Medical College & Research Foundation between December 2015 and December 2016. Diabetes mellitus was diagnosed using 2018 American diabetes association (ADA) diagnostic criteria.[1] Unwilling participants, participants diagnosed as type 1 diabetes mellitus, gestational diabetes mellitus, fibro calculous pancreatitis, pancreatitis, steroid induced diabetes, and participants with known thyroid disorders were excluded from the study. The study commenced after approval from Institutional Ethics Committee and written informed consent was obtained from all study participants. Data was recorded in separate case record forms and the collected data included history, anthropometric parameters [age, gender, weight, height and body mass index (BMI)], clinical examination findings and laboratory parameters [fasting plasma glucose (FPG), 2-hour post prandial glucose (2h-PPG), glycated haemoglobin (HbA1c), triiodothyronine (T3), tetraiodothyronine (T4) and thyroid stimulating hormone (TSH)].Thyroid involvement was assessed using symptoms of thyroid dysfunction and based on laboratory values of T3, T4 and TSH. Participants were categorized to different weight class depending on BMI for Asia pacific individuals.[13]Sample size was calculated as 150 using the formula $4pq/d^2$ where p is the prevalence of thyroid dysfunction among diabetics,[8,14] q is 1-p, d is the precision of error. Data was analysed using R®, nominal variables were compared using independent sample‘t’ test and ANOVA, categorical variables were compared using Chi square test.All values were rounded off to the nearest decimal and are expressed as mean [standard deviation (SD)]. $p<0.05$ was considered statistically significant.

RESULTS

Our study enrolled 150 T2DM patients of which 59.3% (n=89) were females and 40.7% (n=61) were males. 42% (n=63) study participants were in the age group of 51-60 years, 34.7% (n=52) in 61-70 years and least number of participants were in the age group of 41-50 years (11.3%, n=17). 43.3% study participants (n=65) were in the normal weight range, 40% (n=60) were overweight, 15.3% (n=23) were obese 1 and 1.3% (n=2) were obese 2. The mean duration of diabetes among study participants was 13 (5.9) years. 51.3% (n=77) study participants were receiving oral antidiabetic agent alone, 25.3% (n=38) were receiving insulin and 23.3% (n=25) were receiving a combination of both. The baseline parameters of the study participants are demonstrated in table 1. No difference was observed in baseline parameters between genders which is demonstrated in table 2.

Parameter	Mean (SD)
Age (years)	60.1 (7.9)
Weight (Kg)	63.5 (6.3)
Height (cms)	164.4 (6.9)
BMI (Kg/m^2)	23.5 (2.2)
FPG (mg/dl)	183.4 (20.4)
2h-PPG (mg/dl)	279.6 (38.1)
HbA1c (%)	7.7 (0.8)
T3 (ng/ml)	1.3 (0.5)
T4 (µg/dl)	6.8 (2)
TSH (µU/ml)	3 (2.4)

Table 1. Baseline Parameters of the Study Participants

Parameter	Gender	n	Mean (SD)	P
Age (years)	Female	89	60.3 (7.8)	0.8
	Male	61	59.9 (8.3)	
Height (cms)	Female	89	164.6 (7.2)	0.6
	Male	61	164.1 (6.6)	
Weight (Kg)	Female	89	64.3 (6.3)	0.05
	Male	61	62.3 (6.3)	
BMI (Kg/m^2)	Female	89	23.8 (2.4)	0.07
	Male	61	23.1 (1.8)	
FPG (mg/dl)	Female	89	182.2 (19.1)	0.4
	Male	61	185.2 (22.2)	
2-h PPG (mg/dl)	Female	89	276.8 (37.1)	0.3
	Male	61	283.7 (39.3)	
HbA1c (%)	Female	88	7.7 (0.9)	0.4
	Male	61	7.8 (0.7)	
T3 (ng/ml)	Female	89	1.3 (0.5)	0.05
	Male	60	1.4 (0.4)	
T4 (µg/dl)	Female	89	6.8 (2.3)	0.8
	Male	61	6.8 (1.3)	
TSH (µU/ml)	Female	89	3.3 (2.8)	0.05
	Male	61	2.6 (1.5)	

Table 2. Gender Stratified Comparison of Baseline Parameters

Gender stratified comparison of baseline parameters showed no significant difference. Macrovascular complications of diabetes such as ischemic heart disease (IHD), cerebrovascular accidents (CVA), and hypertension (HTN) were seen in 34% (n=51), 28% (n=42) and 61.3% (n=92) participants respectively. Microvascular complications such as retinopathy, nephropathy and neuropathy were seen in 8% (n=12), 6.7% (n=10) and 8% (n=12) participants respectively. The mean duration of diabetes in participants with neuropathy, nephropathy, retinopathy, HTN, IHD and CVA were 14.4 (5.8), 14.1 (7.3), 14.8 (6.8), 15.8 (5.1), 18.2 (4.9) and 12.8 (6.2) years respectively. Mean duration of diabetes in participants without neuropathy, nephropathy, retinopathy, hypertension, IHD and CVA were 12.9 (5.9), 12.9 (5.8), 12.8 (5.8), 8.7 (4.1), 10.4 (4.4), 12.8 (6.2) years respectively. Among the study participants, 96.7% (n=145) did not have symptoms of thyroid dysfunction and 3.3% (n=5) had symptoms of thyroid dysfunction. Among the study participants, thyroid swelling was seen in 6% (n=9), 5.3% (n=8) had visible swelling and 0.7% (n=1) had palpable swelling. Categorizing participants based on laboratory thyroid function tests showed that 83.3% (n=125) were having normal thyroid function, 13.3% (n=20) were having overt hypothyroidism, 2% (n=3) were having subclinical hypothyroidism and 1.3% (n=2) were having overt hyperthyroidism. Categorizing participants based on thyroid swelling demonstrated significant difference in weight (p=0.01), height (p=0.01), BMI (p<0.001), HbA1c (p=0.006), T3 (P=0.002) and TSH (p<0.001) which is demonstrated in table 3. Thyroid function stratified comparison demonstrated significant difference in height (p<0.001), BMI (p<0.001) and FPG (p<0.001) which is demonstrated in table 4.

Parameter	Goitre	n	Mean (SD)	p
Age (years)	No	141	60.4 (7.9)	0.1
	Yes	9	56.2 (8.7)	
Duration of diabetes (years)	No	141	13 (5.8)	0.9
	Yes	9	13.2 (7.8)	
Weight (Kg)	No	141	63.2 (6)	0.01*
	Yes	9	68.8 (8.9)	
Height (cms)	No	141	164.7 (6.7)	0.01*
	Yes	9	158.9 (9.3)	
BMI (Kg/m^2)	No	141	23.3 (1.9)	<0.001*
	Yes	9	27.3 (3.3)	
FPG (mg/dl)	No	141	183.9 (19.6)	0.2
	Yes	9	176.3 (31.4)	
2h-PPG (mg/dl)	No	141	280.5 (36.2)	0.2
	Yes	9	266.1 (61.9)	
HbA1c (%)	No	141	7.7 (0.8)	0.006*
	Yes	8	8.5 (1)	
T3 (ng/ml)	No	140	1.4 (0.4)	0.002*
	Yes	9	0.9 (0.8)	
T4 (µg/dl)	No	141	6.8 (1.6)	0.9
	Yes	9	6.8 (5.1)	
TSH (µU/ml)	No	141	2.8 (1.9)	<0.001*
	Yes	9	7 (4.2)	

Table 3. Comparison of Baseline Parameters Based on Thyroid Swelling

* indicates significant difference between the groups using independent sample t test.

Parameter	Thyroid Function	n	Mean (SD)	P
Age (years)	Normal thyroid function	125	60.7 (7.8)	0.1
	Overt hyperthyroidism	2	48.5 (6.4)	
	Subclinical hypothyroidism	3	59.7 (12.9)	
	Overt hypothyroidism	20	58.2 (7.8)	
Duration of diabetes (years)	Normal thyroid function	125	12.9 (5.7)	0.06
	Overt hyperthyroidism	2	7.5 (2.1)	
	Subclinical hypothyroidism	3	16 (12.2)	
	Overt hypothyroidism	20	13.8 (6.1)	
Weight (Kg)	Normal thyroid function	125	63 (6)	0.3
	Overt hyperthyroidism	2	60.5 (2.1)	
	Subclinical hypothyroidism	3	65 (11.3)	
	Overt hypothyroidism	20	66.6 (7.5)	
Height (cms)	Normal thyroid function	125	165.8 (5.4)	< 0.001*
	Overt hyperthyroidism	2	163.5 (2.1)	
	Subclinical hypothyroidism	3	153.3 (5.8)	
	Overt hypothyroidism	20	157.2 (10)	
BMI (Kg/m^2)	Normal thyroid function	125	22.9 (1.3)	<0.001#
	Overt hyperthyroidism	2	22.5 (0.02)	
	Subclinical hypothyroidism	3	27.5 (2.6)	
	Overt hypothyroidism	20	27 (2.7)	
FPG (mg/dl)	Normal thyroid function	125	187.4 (14.3)	<0.001*
	Overt hyperthyroidism	2	178 (4.20	
	Subclinical hypothyroidism	3	150 (26)	
	Overt hypothyroidism	20	164.4 (34.6)	

2h-PPG (mg/dl)	Normal thyroid function	125	280.5 (36.1)	0.06
	Overt hyperthyroidism	2	253.5 (65.8)	
	Subclinical hypothyroidism	3	269.3 (51.4)	
	Overt hypothyroidism	20	278.3 (47.4)	
HbA1c (%)	Normal thyroid function	125	7.6 (0.7)	0.1
	Overt hyperthyroidism	2	8.8 (0.3)	
	Subclinical hypothyroidism	3	8.2 (1.8)	
	Overt hypothyroidism	19	8.1 (1.2)	

Table 4. Comparison of Baseline Parameters Based on Thyroid Function

*indicates significant difference with participants with normal thyroid function; # indicates significant difference with participants with normal thyroid function & between each other.

No association was observed between gender and type of thyroid dysfunction (p=0.09), treatment of T2DM and type of thyroid dysfunction (p=0.08), thyroid dysfunction and retinopathy (p=0.1; OR–2.8, 95% CI 0.8–10.1), thyroid dysfunction and neuropathy (p=0.1; OR–2.8, 95% CI 0.8–10.1), thyroid dysfunction and nephropathy (p=0.6; OR-0.5, 95% CI 0.1-4.4), hypertension and thyroid dysfunction (p=0.1; OR– 0.5, 95% CI 0.2–1.2), IHD and thyroid dysfunction (p=0.5; OR–0.7, 95% CI 0.3–1.8), history of CVA and thyroid dysfunction (p=0.6; OR–0.8, 95% CI 0.3–2.1). TSH (p<0.001) and HbA1c (0.02) showed significant difference between groups when participants were categorized based on BMI; these are demonstrated in table 5.

Parameter	BMI	n	Mean (SD)	p
TSH (µU/ml)	Normal	65	2.3 (1.1)	< 0.001*
	Overweight	60	2.4 (1.3)	
	Obese 1	23	6.3 (3.6)	
	Obese 2	2	8.6 (0.8)	
HbA1c (%)	Normal	65	7.6 (0.6)	0.02#
	Overweight	60	7.7 (0.6)	
	Obese 1	22	8 (1.4)	
	Obese 2	2	9.1 (1.6)	
Duration of diabetes (years)	Normal	65	13.2 (5.2)	0.9
	Overweight	60	13 (6)	
	Obese 1	23	12.6 (7.4)	
	Obese 2	2	13.5 (5)	

Table 5. Comparison of Mean TSH, HbA1c and Duration of Diabetes Based on BMI

* indicates significant difference between normal weight, obese 1, and obese 2 and also between overweight, obese 1 and obese 2, # indicates significant difference between normal, obese 1 and obese 2 and also between overweight and obese 2.

Analysis of thyroid function among study participants based on their ADA glycemic goal for FPG, PPG and HbA1c showed significant association between thyroid dysfunction and ADA glycemic goal for FPG (p<0.001) which could indicate the higher number of participants who did not attain ADA glycemic control for FPG with overt hypothyroidism (n=16). None of the study participants attained ADA glycemic goal for 2h-PPG (< 180 mg/dL), chi square test did not show any significant association (p=0.1). No association was observed between attained ADA glycemic goal for HbA1c (<7%) and thyroid dysfunction.

ADA Glycemic Goal FPG (80-130 mg/dl)	Thyroid Function Among study Participants				Total
	Normal	Overt Hyperthyroidism	Subclinical Hypothyroidism	Overt Hypothyroidism	
Attained glycemic goal	0	0	1	4	5
Not attained glycemic goal	125	2	2	16	145
Total	125	2	3	20	150

Table 6. Association between ADA Glycemic Goal (FPG) and Thyroid Dysfunction

Significant association was observed between ADA glycemic goal for FPG and thyroid dysfunction (p<0.001).

ADA Glycemic Goal HbA1c (< 7%)	Thyroid Function among Study Participants				Total
	Normal	Overt Hyperthyroidism	Subclinical Hypothyroidism	Overt Hypothyroidism	
Attained glycemic goal	15	0	1	5	21
Not attained glycemic goal	110	2	2	15	129
Total	**125**	**2**	**3**	**20**	**150**

Table 7. Association between ADA Glycemic Goal (HbA1c) and Thyroid Dysfunction

No association was observed between ADA glycemic goal for HbA1c and thyroid dysfunction (p=0.3).

DISCUSSION

Among 150 study participants, 89 (59.3%) were females and 61 (40.7%) were males which could be due to the higher reported prevalence of T2DM in female participants,[14–17] or could be due to higher female to male ratio in Kerala in contrast to the national average.[18] This could also be due to the neglected and untreated condition gestational diabetes mellitus which predispose to development of diabetes mellitus in later life.[19] Higher levels of sex hormone binding globulin in females could be another reason for higher prevalence of T2DM in females.[20] The mean age of the study participants was ~ 60 years which is higher compared to reports of higher prevalence of T2DM among young individuals.[21] This could be due to the enrolment of participants from outpatient department, where the regular patients are more frequently encountered than the new and young patients. 43% of the participants were in the normal weight, 56% were having higher BMI. Diabetic participants have been reported to have higher BMI[15,22] and strong association between T2DM and obesity have been reported. The possible mechanisms is the release of non-esterified fatty acids, hormones and inflammatory cytokines due to reduced insulin secretion causing uptake of non-esterified fatty acids by peripheral tissues further reducing insulin secretion.[23] This also explains the significantly higher HbA1c in obese individuals. The mean duration of diabetes in our study participants was 13 years. This could be due to the higher life expectancy of Keralites which is comparable to high income countries or due to easily accessible healthcare due to policies of the State government[24] and also due to the high literacy among Keralites leading to better awareness regarding non-communicable diseases. Only 3% of participants had symptoms of thyroid dysfunction, 6% participant had thyroid swelling. Since the clinical symptoms of hypothyroidism are nonspecific they are difficult to notice clinically especially in elderly. This could also be due to the association of medical and psychiatric conditions with thyroid disorders and also due to the long latency of development of symptoms.[25]Among the study participants 13.3% (n=20) had overt hypothyroidism, 2% (n=3) had subclinical hypothyroidism and 1.3% (n=2) had overt hyperthyroidism. This was higher than previous foreign reports suggesting a prevalence of 12-14%[8,26] and lower than an Indian study reporting a prevalence of 31%.[27] Diabetics are at higher risk of developing thyroid disorders[27]and Asian diabetics are reported to be at an even higher risk possibly due to the iodization of salt leading to excess iodine consumption and subsequent hypothyroidism,28 regular consumption of goitrogens in diet and also due to deficiency of micronutrients such as selenium and iron[29].

Among the participants with thyroid dysfunction, 80% were females, which is similar to previous studies[27–29] though it has not been described why thyroid dysfunction is more common in females. Our study did not demonstrate any significant difference in duration of diabetes between various categories of thyroid dysfunction (p=0.06) which is similar to previous studies.[30,31] Though insulin resistance (IR) has been associated with thyroid dysfunction[9], duration of IR or diabetes mellitus has not been shown to have association with thyroid dysfunction. Our study demonstrated significantly higher TSH in obese compared to overweight and individuals with normal BMI, which could be due to the basal metabolism regulating, thermogenic, lipid and glucose metabolizing, satiety inducing effects of thyroid hormones which are significantly reduced with elevation of TSH.[32] This could be due to the inverse relationship between thyroid hormones and leptin[33] (TSH stimulates leptin production) which regulates energy homeostasis by its action on central nervous system and feeding behaviour. We did not observe association between micro and macrovascular complications of T2DM and thyroid status of the study participants in contrast to previous reports.[34,35] This could be due to the high prevalence of thyroid disorders among Keralites making them extremely common among T2DM patients when compared to other complications of DM.[36] Significantly higher participants who did not attain ADA glycemic goal had overt hypothyroidism which is similar to previous reports suggesting altered thyroid hormones in participants with poor glycemic control[37]which is thought to be due to abolition or blunting of nocturnal TSH peak and reduced response of TSH to TRH and due to the impairment of peripheral conversion of T4 to T3 which normalizes with glycemic control.

CONCLUSION

56.7% participants were having above normal BMI. 16.7% T2DM patients had some form of thyroid dysfunction and thyroid dysfunction was more common in females. Among the study participants, 13.3% (n=20) had overt hypothyroidism, 2% (n=3) had subclinical hypothyroidism and 1.3% (n=2) had overt hypothyroidism, 2% (n=3) subclinical hypothyroidism and 1.3% (n=2) overt hyperthyroidism. Significant difference in weight (p=0.01), BMI (p<0.001) and HbA1c (p=0.006) was observed when participants were categorized based on thyroid swelling. Significant difference in BMI (p<0.001) and FPG (p<0.001) was observed when participants were categorized based on type of thyroid dysfunction. Significant difference in thyroid stimulating hormone (p<0.001) and HbA1c was seen when participants were categorized based on BMI. Association was observed between ADA glycaemic goal and type of thyroid dysfunction (p<0.001). Failure to recognize the presence of thyroid dysfunction among T2DM patients may be a primary cause of poor management of diabetes. We recommend screening and regular monitoring of thyroid dysfunction in T2DM patients.

ABBREVIATIONS

2-h PPG- 2-hour Post Prandial Glucose
ADA- American Diabetes Association
ANOVA- Analysis of Variance
BMI- Body Mass Index
CVA- Cerebro-Vascular Accident

DM- Diabetes Mellitus
FPG- Fasting Plasma Glucose
HbA1c- Glycated Haemoglobin
HTN- Hypertension
IHD- Ischemic Heart Disease
IR- Insulin Resistance
OR- Odds Ratio
SD- Standard Deviation
T2DM- Type 2 Diabetes Mellitus
T3- Triiodothyronine
T4- Tetraiodothyronine
TRH- Thyrotropin Releasing Hormone
TSH- Thyroid Stimulating Hormone.

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