Thyroid Science 6(4):1-9, 2011

www.ThyroidScience.com

Clinical and Laboratory Studies

The Impact of Diabetes on Thyroid Dysfunction and Outcomes in a Native Indian Female Population

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Received: March 8, 2010
Accepted: March 31, 2010

Abstract. **Introduction**: In the present study, the prevalence and pattern of thyroid dysfunction in an Indian female population with type 2 diabetes mellitus (T2D) were assessed. The aim was to find the correlation and comparison between these two major metabolic disorders. **Methods**: The study was a population-based survey of the prevalence of thyroid dysfunction in the T2D population. Participants in the study were 137 eligible females aged between 30-to-70 years. The biochemical parameters were body mass index (BMI), glycemic control (fasting and post prandial blood glucose levels, glycated haemoglobin A1c), and a thyroid profile (TSH, free T_3, and free T_4). These parameters were measured and compared with the normal population. Medication compliance was also considered. **Results**: Patients taking medications for both the conditions (T2D and hypothyroidism[HO]) showed controlled biochemical investigations compared to patients suffering from individual disorders; patients with both disorders had therapeutic stability. **Conclusion**: This study suggests that in the female population, T2D and HO are prevalent both individually and jointly. Further, there seems to be a good comparison between patients who have one of the metabolic disorders and those who have only one of them. The significant correlation positive between insulin use by T2D patients and disease complications was positive, and the correlation between hyperthyroidism and BMI was significantly negative. Age positively correlated with HbA1c and T2D duration. A significant correlation between T2D and HO was not established in this study. However, unsuspected/undiagnosed HO may be a matter of consideration for T2D patients.

Keywords • type 2 diabetes • hypothyroidism • metabolic disorder • prevalence • body mass index

Introduction

Type 2 diabetes (T2D) accounts for most individuals with non-autoimmune forms of diabetes. The spectacular increase in the prevalence of T2D worldwide is well documented.[1] Early identification is an important tool for the management of diabetes, as insulin resistance or relative insulin deficiency may lead to diverse complications of diabetes.[2]

Thyroid hormones play an indispensable role in various metabolic processes in the human body.[3] Hypothyroidism and hyperthyroidism are the main clinical conditions that affect the basal metabolic rate. Thyroid immunity is known to be more common in the female population. The higher incidence among females may be attributed to inhibition of disease activity by androgens and exacerbation by estrogens.[4,5]

Diabetes mellitus and thyroid diseases are the two most common endocrinopathies seen in the adult population. Excess or deficiency of either insulin or thyroid hormones can result in functional abnormalities of one another, as both of them are closely involved in cellular metabolism.[6] Possibly, thence, diabetes and thyroid disorders have a propensity to appear together in patients.[7,8] Patients with T2D commonly display the symptoms of hypothyroidism, and symptoms of hyperthyroidism have been documented in patients with type 1 diabetes.[8,9] Since there may be a link between diabetes and thyroid diseases, the American Diabetes Association (ADA) has proposed that people with diabetes be checked for thyroid disorders.[10]

In the light of the above facts, our objectives were to find out the prevalence of thyroid dysfunction in a T2D female population. An effort was made to compare and correlate these two metabolic disorders

by taking into consideration various biochemical parameters. Pharmacological treatment compliance in each group was studied to determine the stability in terms of change in dose or type of medication for each subject.

Materials and Methods

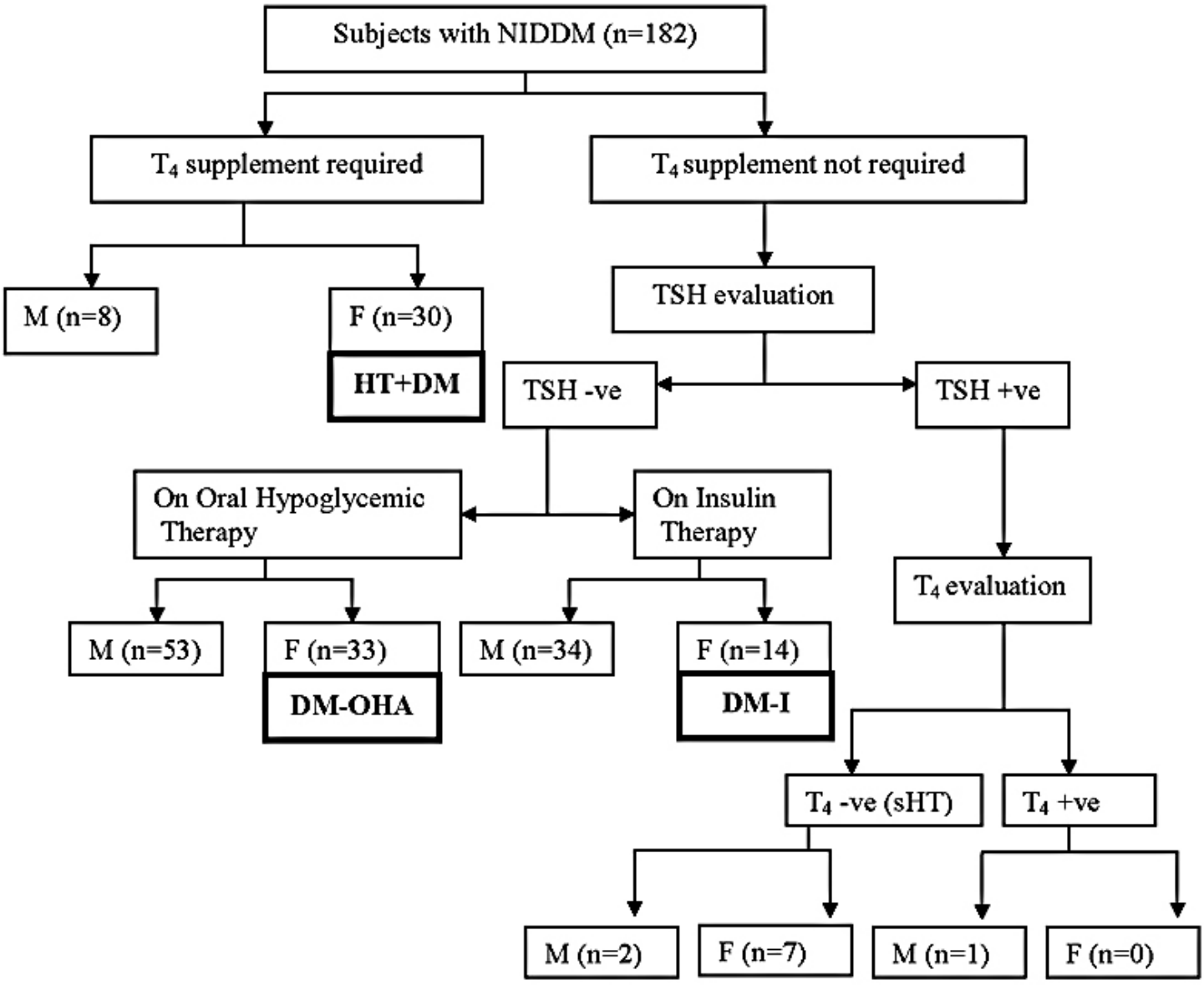
The protocol for the present study was approved by the human ethical committee of L.M. College of Pharmacy, Ahmedabad. All patients were given verbal and written information about the study prior to providing written consent.

A total of 182 female T2D patients were screened for thyroid dysfunction to find the prevalence of hypothyroidism and hyperthyroidism among them. Eligible for inclusion in the study were 77 female patients with a previously established diagnosis of T2D.

Patients were further grouped according to their pharmacological treatment. Thirty subjects were on both thyroxine therapy and diabetes medications. These 30 patients were classified as HT+DM. Thirty-three diabetes patients were on oral hypoglycemic agents, and 14 were on insulin therapy. These patients were classified as DM-OHA and DM-I, respectively.

Screening for Type 2 Diabetes

T4 = Thyroxine, M = male, F = female, sHT = subclinical hypothyroidism



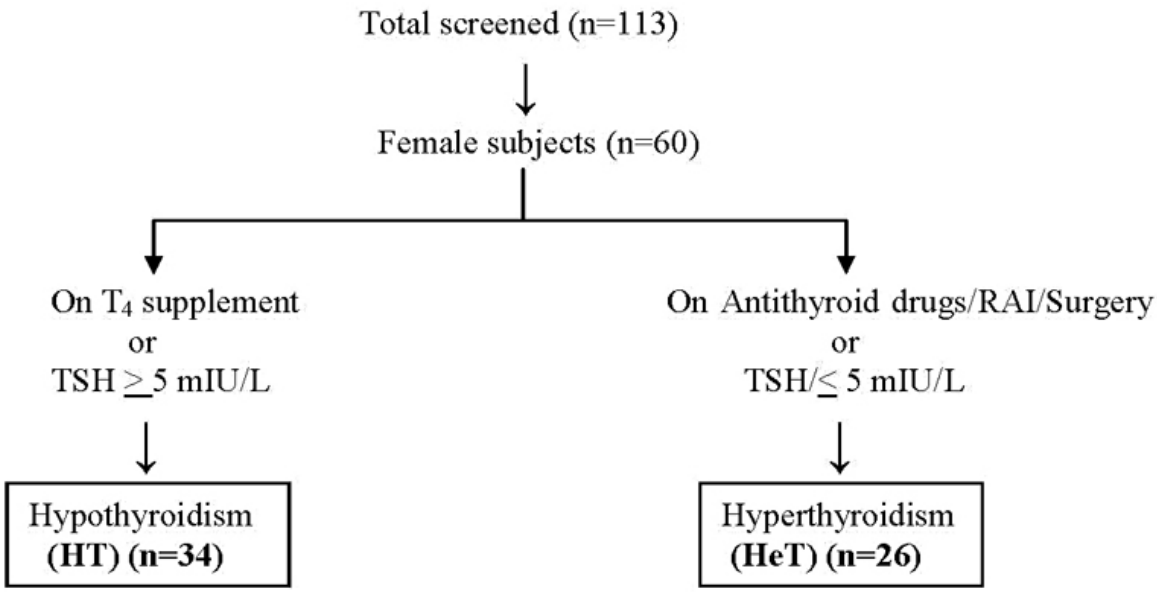
non-probability groups basis.

An effort was made to match groups of patients based on basic confounders like age, sex, and socio-economic status. Diagnosis of disease condition(s) was required to have been established at least two years before a patient was admitted to the study. Patients were excluded if they had a history of ketoacidosis, impaired hepatic function, or severe anemias.

Pharmacological Treatment Compliance. Effectiveness of treatment was assessed at each study visit by detailed interviews of patients by the investigators, a probing questionnaire, and clinical and laboratory findings. Changes, if any, in prescription or worsening of diabetic and/or thyroid complications

Screening of Thyroid Dysfunction in Female Subjects

RAI = radioactive iodine



were assessed for each patient. A change in dose or type of medication was considered instability. Treatment was graded based on changes made at six-month intervals. Therapeutic stability was assessed by the grade for a total of two years of treatment. Medication compliance was assessed by counting the number of pills left and comparing the number with the number of pills scheduled the time of specified clinic visits.

Baseline Characteristics. Baseline characteristics of all the subjects were composed by asking them to fill out the questionnaire pertaining to age, sex, years since disease condition(s) diagnosed, family history, complications associated with the disease(s), and food habits. Family history and complications were graded as per the stages of the disease(s) development.

Anthropometric Measurements. Body weight in light clothes was measured using a Krups weighing scale (Jammu & Kashmir, Srinagar, India) and height to the nearest 0.5 cm using portable stadiometers (Galaxy Scientific, New Delhi, India). Participants stood upright on a flat surface with the back of the heels and the occiput on the stadiometers. Body mass index (BMI) was calculated as the weight (in kilograms) divided by height squared (in meters).

Biochemical Investigations. Assessment of glycemic control (HbA1c, fasting, and post-prandial blood glucose [FPG and PPBS, respectively]) and thyroid profile [TSH, T_3, T_4 levels] were assessed at an interval of six months for two years prospectively.

All plasma levels were determined after a 10-hour overnight fast except PPBS, which was determined 2 hours after lunch. Venous blood samples were drawn from all patients between 08:00 and 09:00 hours. Plasma was obtained by the addition of Na-EDTA, 1 mg/mL, and centrifuged at 3000 g for

15 min at 4°C. Immediately after centrifugation, the plasma samples were frozen and stored at -80°C for ≤ 3 months. Plasma glucose levels were assayed by the hexokinase method (Shimadzu UV double beam spectrophotometer UV-1601, Columbia, USA). Glycated haemoglobin level (HbA1c) was measured by high-pressure liquid chromatography (HPLC) (Bio Rad D-10, Vadodara, Gujarat, India) techniques. Serum T_3, T_4, and TSH concentrations were estimated by enzymatic electrochemiluminescent immunoassay method (Abbott Architect i 2000, Abbott Laboratories, Abbott Park, USA).

Statistical Analysis. All the data are represented as mean ± SEM unless otherwise specified. One-way ANOVA followed by the Tukey-Kramer multiple comparison test was used to compare the data using Graph Pad Instat 3.01 software (La Jolla, CA, USA). Pearson product moment correlation was used to analyze the relationship between interdependence of laboratory findings in HT+DM subjects and Sigma Stat 2.03 (San Rafael, CA, USA) was used to correlate it. A value of $p < 0.05$ was considered as statistically significant.

Results

Pharmacological treatment for T2D subjects is shown below in Table 1: 74.8% of patients were on oral hypoglycemic agents, 28% were on insulin preparations, 72.9% were on statins, 38% were on fibrates, and 81% were on aspirin. Levothyroxine was take by 98.4% of subjects with hypothyroidism. Of the hyperthyroid patients, 86% were on thioamides, 54% were treated with radioactive iodine, and 2% had thyroid surgery. Two patients with hyperthyroidism were shifted to hypothyroidism and two with hypothyroidism were shifted to hyperthyroidism.

The average stability of patients complying with their therapy is demonstrated in Figures 1 & 2. Change in type or dose of medication was considered instability. It is clear from the graph that HT+DM subjects were found quiet stable (85% for anti-diabetes therapy and 92.9% for thyroid dysfunctioning therapy) as compared to individual in other groups, i.e. DM-OHA (68.8%), DM-I (58.9%), HT (56.6%), and HeT (45.2%) of patients.

Prevalence. Mean and standard error of mean were stratified by diabetic and/or thyroid dysfunctioning status. The incidence of thyroid dysfunctioning among T2D subjects (age 30-70 years) from the study community are presented in Table 1.

Table 1. Prevalence of thyroid dysfunctioning in T2D patients.

Gender	DM-OHA	DM-I	HT	HeT	HT+DM
Male n (%)	53 (61.18)	34 (70.83)	22 (39.29)	31 (54.39)	8 (21.05)
Female n (%)	33 (38.82)	14 (29.17)	34 (60.71)	26 (45.61)	30 (78.95)
Male / Female ratio	1.58	2.43	0.65	1.19	0.27

Values are number of subjects with percentage in parenthesis. DM-OHA = T2D subjects on oral hypoglycemic therapy, DM-I = T2D subjects on insulin therapy, HT = hypothyroid subjects, HeT = hyperthyroid subjects, HT+DM = subjects with hypothyroidism and T2D.

Among total screened 182 T2D subjects, 77 were female (42.31%), which were included into the study. As can be noted in the Table 1, the majority cases of HT+DM were found in females compared to males (30 vs. 8) reflecting female preponderance to be fairly high (78.95%) in HT+DM subjects.

Baseline characteristics. Baseline characteristics of randomized female subjects are presented in Table 2. BMI, a measure of obesity was associated with development of one or both metabolic disorders. BMI value of HT was incredibly high (31.8 kg/m^2), while HeT group had lower values (21.3 kg/m^2) when compared with the other groups. The age standardized prevalence rates of obesity (BMI) standardized prevalence rates of obesity (BMI) stratified by the presence of one or both metabolic disorders comparing the study population with the normal control female subjects has been presented in Figure 3.

As demonstrated in Figure 3, the burden of obesity was high in the study population, especially in hypothyroid females (82.4%). Higher incidences of diabetic secondary complications were eminent (22.34% higher) in DM-I group, which was statistically significant, when compared with the HT+DM subjects. On the other hand, lack of family history pervasiveness and minimal incidences of diabetes and/or thyroid complications were observed in HeT and HT+DM subjects, respectively (Table 2).

Glycemic control profile. As shown in Table 3, glycemic control in terms of FBS and PPBS, was found statistically significant in DM-OHA, DM-I

and HT+DM group when compared with the normal group. group. However, rise in glucose levels was found clinically non-significant as these values were within the normal range (110-150 mg/dL). It was 112.5 and 153 mg/dl for FBS and PPBS respectively in HT+DM subjects. HbA1c, a major predictor of

Table 2. Baseline characteristics of patients.

Groups	DM-OHA	DM-I	HT	HeT	HT+DM
Age (years)	57.21 ± 1.28	54.14 ± 2.36	47.74 ± 1.91	47.65 ± 1.66	50.77 ± 1.73
F (n%)	38.82	29.17	60.71	45.61	78.95
BMI (kg/m^2)	27.55 ± 0.99	28.52 ± 0.97	31.8 ± 1.15	21.25 ± 0.44*	29.99 ±1.01
Duration (years)					
DM	10.46 ± 1.81	13.57 ± 1.91	-	-	10.43 ± 1.42
TD	-	-	6.41 ± 0.55	3.88 ± 0.44	8.48 ±1.26
FH	1.13 ± 0.17	1.86 ± 0.31	2.00 ± 0.2	0.27 ± 0.09	1.59 ± 0.20
DC	1.33 ± 0.18	1.79 ± 0.28*	0.5 ± 0.096	0.85 ± 0.15	0.4 ± 0.15
FC (KCal)	1926.08 ± 86.13	48.21 ± 88.71 16	1922.55 ± 57.66	1570.46 ± 73.74	1844.46 ± 58.44

All the data are expressed as mean ± SEM. DM-OHA, DM-I, HT and HeT grouped data are compared with the HT+DM. whereby, *p < 0.05.

F = female, TD = thyroid disorder, FH = family History, DC = disease complications, FC = food calorie intake, DM-OHA = T2D subjects on oral hypoglycemic therapy, DM-I= T2D subjects on insulin therapy, HT= hypothyroid subjects, HeT= hyperthyroid patients, HT+DM = subjects with hypothyroidism and T2D.

diabetes has been studied in all the groups. Although, it is very clear form our findings that HbA1c parameter did not change remarkably in the subjects having both T2D and HT complications (7.85%) as compared to individual groups viz., DM-OHA (9.08%) and DM-I (8.38%). The proportion of population showing HbA1c values higher than normal levels has been represented in Figure 4. As can be seen from graph, it is comparatively higher in diabetic subjects (DM-OHA and DM-I, 87.5% and 78.6% respectively) as compared to HT+DM subjects (73.3%).

Thyroid profile. Thyroid profile included measurements of T_3, T_4 and TSH levels. As can be seen in Table 3, T_3 and T_4 levels were significantly high in HeT subjects as compared to normal patients ($p < 0.05$). At the same time, these levels remained significantly low in HT subjects when compared with normal subjects. However, there was a remarkable increase in TSH levels ($p < 0.05$) observed in the HT group. TSH levels remained significantly low in HeT group subjects. HT+DM subjects showed almost normal thyroid profile values of compared to individual disease groups in the study. The percentage of subjects in each group whose TSH values were outside the reference range (0.5-4.0 mIU/L) are represented in Figure 5.

As shown in Figure 5, TSH levels were found above normal range in 56% population of HT subjects and 38% population showed below normal levels in HeT subjects. However, only 20% population of HT+DM group showed altered TSH values. Further, 33% DM-OHA subjects showed higher than normal values of TSH in a prospective study during their two years follow-up. However, the mean value lies within normal range, but overall TSH levels were slightly above than upper limits of TSH values (5 mIU/L).

In addition to above, as shown in Table 4, age, diabetes duration and HbA1c values showed positive correlation coefficients with p values below 0.05. They tend to increase together, revealing that age is a predisposing factor to diabetes mellitus.

Thus, the data demonstrate association of diabetes with thyroid dysfunction to a certain extent. It is particularly notable that simultaneous control of these two major metabolic disorders, namely T2D and thyroid dysfunction, is protective against diabetic complications.

Discussion

Therapy of each group was assessed retrospectively from records for two years. Also, therapeutic

changes were noted in the patient population during the prospective designed study. Depending upon the grades provided for each therapy, grade changes were noted for data from the last two years. DM-OHA and DM-I subjects showed significant variation in antidiabetic therapy medication and dosage

Table 3. Biochemical Investigations.

Parameter	Normal	DM-OHA	DM-I	HT	HeT	HT+DM
FBS (mg/dL)	85.8±1.75	130.08±6.37$^{\#\#}$	134.04±6.09$^{\#\#}$	92.9±2.24	89.04±3.72	112.5±12.6$^{\#\#}$
PPBS (mg/dL)	113.93±1.7	180.65±9.66$^{\#\#}$	168.73±9.54$^{\#\#}$	107±2.5	107.78±2.9	153±10.7$^{\#\#}$
HbA1c (%)	5.91±0.13	9.08±0.34$^{\#\#}$	8.38±0.44$^{\#\#}$	6.14±0.17	6.06±0.09	7.85±0.26$^{\#\#}$
TSH (mIU/L)	2.7±0.28	4.07±0.32	2.86±0.39	6.94±0.79**$^{\#}$	0.82±0.19	4.89±1.36
Serum T_3 (mIU/L)	4.47±0.32	1.55±0.38	1.41±0.34	1.49±0.3	31.11±10.0**	2.26±0.48
Serum T_4 (mIU/L)	24.89±13.42	8.24±0.92	9.02±0.69	9.09±0.39	16.93±1.08*	7.33±0.59

All results are expressed as Mean ± SEM.
DM-OHA, DM-I, HT and HeT grouped data are compared with the HT+DM. *p < 0.05, **p < 0.01.
DM-OHA, DM-I, HT, HeT and HT+DM grouped subjects were compared with the normal subjects' population.
#*p* < 0.05, ##*p* < 0.01, ###*p* < 0.001.
FBS = fasting blood sugar levels, PPBS = post-prandial blood sugar levels, HbA1c = glycated Haemoglobin A1c.
TSH= thyroid stimulating hormone, T3= Tri-iodo thyronine, T4= Thyroxine. DM-OHA= T2D subjects on oral hypoglycemic therapy, DM-I= T2D subjects on insulin therapy, HT= hypothyroid subjects, HeT= hyperthyroid subjects, HT + DM = subjects with hypothyroidism and T2D.

when compared with the HT+DM subjects. Similarly, HT and HeT subjects underwent a wide range of changes in therapy within two years' duration as compared to HT+DM subjects. These facts may possibly draw our attention towards a mutual role of thyroid and insulin hormones in governing and maintaining the status of the two diseases.

High prevalence rates of T2D and hypothyroidism have been reported in different populations,[11,12] but the full impact of the development of these two metabolic abnormalities appears to be evolving. The female predominance of developing T2D and thyroid dysfunction simultaneously is 78.95% (30 out of 38). This finding supports the higher-than-normal prevalence of these two major metabolic disorders at the same time in the female population.[8] This may also support the observation that thyroid autoimmunity is common in T2D female patients.[13] In the present study, we observed a high prevalence of both disorders together in the female population of Gujarat. Hypothyroidism was the more commonly observed thyroid dysfunction in HT+DM patients; hyperthyroidism developed in only one patient with T2D.

BMI, a major predictor of obesity,[14] was higher in the study population, except that of hyperthyroid subjects. Their lower BMI may have been due to increased metabolism in hyperthyroidism. Decreased basal metabolic rates (BMR) in hypothyroid subjects may also have been responsible for the increased BMI in this study population.

Nonetheless, obesity is a major risk factor for T2D and hypothyroidism.[15] It has been demonstrated in other studies that deterioration of glucose tolerance is associated with an increase in obesity for both the male and female population.[16] A strong positive family history observed in our study might have played an important role in the development of these hormonal metabolic disorders and supports the observations of other investigators.[17,18]

Development of secondary complications in diabetes was more common among the DM-OHA and DM-I subjects, as compared to HT+DM subjects. This leads to a thought that hypothyroidism may decrease insulin requirements and thereby protect against development of harmful consequences of diabetes.[19]

It is particularly notable that simultaneous control of these two metabolic disorders is beneficial in reducing glucose tolerance as evident by HbA1c values in this study population. In one case study, as thyroid hormone levels moved into the reference

range, glycated albumin and glycated haemoglobin returned to their normal relative ratio after three months.[20] Our study also supports the report that HbA1c values are controlled in HT+DM patients.

Table 4. Interdependence of parameters in HT+DM subjects.

	Age	BMI	DM duration	TD duration	HbA1c	TSH
Age	1.00	-0.20 (0.298)	0.53 (0.00345)	0.05 (0.811)	0.67 (0.0000503)	-0.24 (0.212)
BMI		1.00	-0.27 (0.155)	0.13 (0.492)	-0.27 (0.143)	-0.15 (0.424)
DM duration			1.00	0.30 (0.114)	0.04 (0.828)	-0.08 (0.684)
TD duration				1.00	-0.13 (0.514)	-0.13 (0.494)
HbA1c					1.00	-0.25 (0.178)

Pearson correlation coefficient test was applied for HT+DM group. BMI = body mass Index, DM = T2D, TD = thyroid dysfunction, HbA1c = glycated hemoglobin A1c. All data are shown as correlation coefficients with *p* values in parenthesis. The pair of variables with positive correlation coefficients and *p* values below 0.050 tends to increase together. For the pairs with negative correlation coefficients and *p* values below 0.050, one variable tends to decrease while the other increases. For pairs with *p* values greater than 0.050, there is no significant relationship between the two variables.

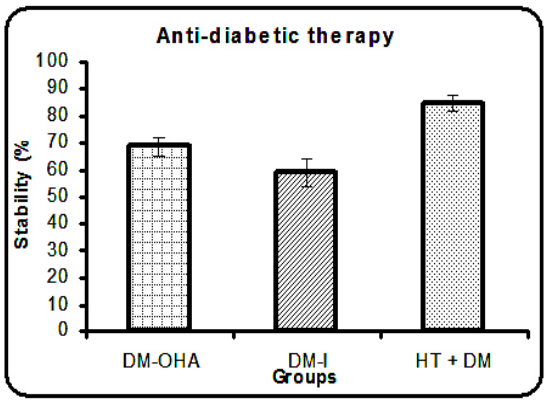


Figure 1. Stability of Anti-diabetic therapy in T2D population. All data are shown in its mean values. DM-OHA = T2D subjects on oral hypoglycemic therapy, DM-I = T2D subjects on insulin therapy, HT+DM = subjects with hypothyroidism and T2D.

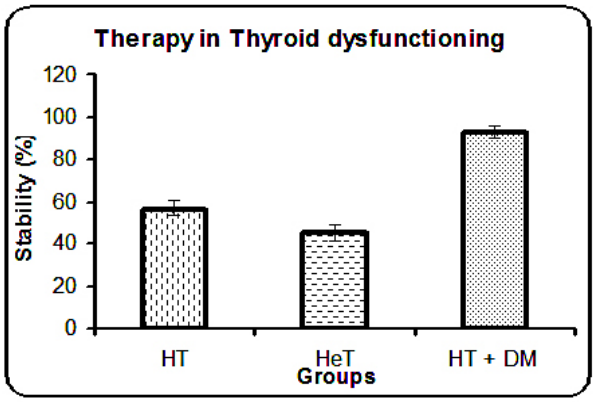


Figure 2. Stability of therapy in thyroid dysfunctional population. All data are shown in its mean values. HT = hypothyroid patients, HeT = hyperthyroid patients, HT+DM = subjects with hypothyroidism and T2D.

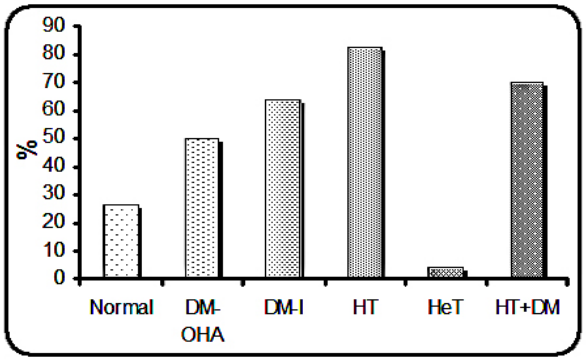


Figure 3. Prevalence (/100) of subjects with BMI >/= 27 kg/m^2. All the data are shown in its mean values. DM-OHA = T2D subjects on oral hypoglycemic therapy, DM-I = T2D patients on insulin therapy, HT = hypothyroid patients, HeT = hyperthyroid patients, HT+DM = subjects with hypothyroidism and T2D.

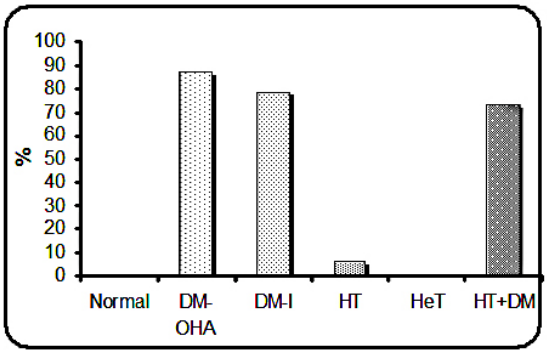


Figure 4. Proportion (/100) of subjects with HbA1c >/= 7%. All the data are shown in its mean values. DM-OHA = T2D subjects on oral hypoglycemic therapy, DM-I = T2D subjects on insulin therapy, HT = hypothyroid subjects, HeT = hyperthyroid subjects, HT+DM= subjects with hypothyroidism and T2D.

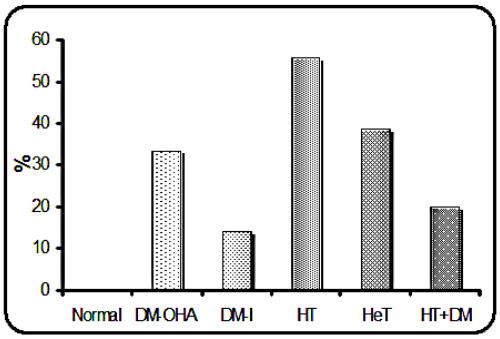


Figure 5. Prevalence (/100) of patients with TSH < 0.5 or > 5 mIU/L. All data are shown in its mean values. DM-OHA = T2D patients on oral hypoglycemic therapy, DM-I = T2D patients on insulin therapy, HT = hypothyroid patients, HeT = hyperthyroid patients, HT+DM = patients with hypothyroidism and T2D.

It has been speculated that serum T_3 levels, basal TSH levels, and the TSH response to thyrotropin releasing hormone (TRH) might be affected by the glycemic status of euthyroid individuals who have T2D[21,22]

In the present study, we observed higher TSH levels ($p < 0.05$) in diabetic subjects receiving oral hypoglycemic medications. Therefore, long-term usage of sulphonamides may lead to the development of hypothyroidism. It is possible, though, that an underlying mechanism could not be established at this point of time; blockade of K_{ATP} by sulphonylureas may reduce the Ca^{++} entry inside the cell and thereby slow down cellular metabolism and lead to conditions like hypothyroidism.[23]

In our study, we found that there is interdependence between insulin and thyroid hormone for normal cellular metabolism. It is apparent, then, that diabetes mellitus and thyroid diseases can mutually influence each other's pathological progress. In one study, after introduction of substitution therapy with levothyroxine, decreased insulin resistance was established.[24,25] Similarly, patients who have both disorders are relatively stable considering their diabetes and thyroid profiles. Thus, thyroid hormone therapy may reduce patients' complications associated with T2D.

Conclusion

Thyroid disorders are quite prevalent in female population of India. There appears to be a higher than normal occurrence of thyroid disorders in people with T2D, with hypothyroidism being the most common. An overactive role of thyroid gland may increase the insulin requirements, but an under active thyroid gland may decrease insulin requirements. Thus, there seems to be a good comparison between hypothyroidism and T2D patients. However, a significant correlation between them could not be established by our study. Further, it is suggested that unsuspected or undiagnosed subclinical hypothyroidism is likely to affect the diabetes status.

Acknowledgements

The authors acknowledge the staff of Gujarat Endocrine Centre, Ahmedabad, especially the guidance of Dr. Parag Shah, M.D., D.M., D.N.B. (Endocrinology) without whose support this work would not have been possible. The present study is supported by the financial assistance of Rameshwardasji Birla Smarak Kosh, Mumbai.

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