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Frequency and predictors of hyperglycemia in patients with various thyroid disorders attending a tertiary hospital of Bangladesh.

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Abstract

Thyroid diseases and diabetes mellitus are the two most common endocrine disorders encountered in clinical practice having a mutual influence on each other, and an association between both conditions has long been reported. This cross-sectional study aimed to explore the frequency of hyperglycemia among newly detected patients with thyroid disorders. Four hundred subjects, newly diagnosed with different forms of thyroid disorders, previously not known to have diabetes or prediabetes, underwent a standard oral glucose tolerance test (OGTT). Plasma glucose values were assessed by the glucose-oxidase method. Out of them, 211 (52.7%) subjects were found to have glucose intolerance (33.5% prediabetes and 19.3% diabetes). Subjects with glucose intolerance had higher mean age, body mass index (BMI), waist circumference, systolic BP, free T4, and lower TSH than euglycemic ones. No statistical difference in glycemic status was observed among the hypothyroid, hyperthyroid, and euthyroid groups. Having a family history of hypertension and abdominal obesity were associated with significantly higher odds of glucose intolerance in the study subjects. Glucose intolerance is frequently found in patients with thyroid disorders. This study emphasizes the importance of screening for glucose intolerance among patients with thyroid disorder.

Keywords: diabetes, glucose intolerance, thyroid dysfunction, hyperthyroidism, hypothyroidism

Introduction

Thyroid disorders and diabetes mellitus are two of the most common endocrine conditions, occurring with greater frequency along with each other (1). Insulin and thyroid hormones are intimately involved in cellular metabolism and thus excess or deficit of either of these hormones can result in the functional derangement of the other (2). Both hypo- and hyper-functioning thyroid gland influence carbohydrate metabolism at the level of pancreatic islets and glucose-utilizing target tissues, imparting important therapeutic and diagnostic implications (3). Thyroid hormones are positively associated with insulin resistance not only in diabetic patients but also in subjects with a normal glucose tolerance (4).

While Graves' disease may be associated with type 1 diabetes in autoimmune polyglandular syndrome, thyrotoxicosis by itself is diabetogenic. Variable glucose intolerance is seen in up to 50% of patients with Graves' disease and frank diabetes occurs in 2-3% of hyperthyroid patients (2). On the other hand, subjects with overt and subclinical hypothyroidism demonstrated both insulin resistance and diminished early insulin secretory response (5, 6, 7, 8). Moreover, the frequency of metabolic syndrome was found to be higher in both subclinical and overt hypothyroidism compared to healthy controls (9).

Very limited data are available regarding the frequency of hyperglycemia among patients with thyroid disorders both in our country and internationally. The current study was undertaken to know the frequency of glucose intolerance in newly detected patients with various thyroid disorders.

Methods

This cross-sectional study was conducted at the Endocrine Outpatient Department (OPD) of a tertiary hospital of Bangladesh from March 2015 to May 2015, with the approval of the Institutional Review Board of the institute. Newly detected adult (≥18 years) patients with various forms of thyroid disorders attending the OPD were considered as the study population and samples were collected consecutively by purposive sampling technique. Thyroid function tests were interpreted according to the normal range of the laboratory (TSH: 0.35-5.5 μIU/mL, FT4: 0.80-1.80 ng/dL) and classified into three groups: hypothyroid, hyperthyroid and euthyroid, according to the criteria set by American Thyroid Association (10, 11). Patients with normal thyroid function but having structural thyroid abnormality such as diffuse or nodular goiter and thyroid malignancy were grouped under euthyroid thyroid disorder group. Patients with diagnosed thyroid disease on treatment, patients with known diabetes or prediabetes, patients with acute illness (sepsis, acute myocardial infarction, severe heart failure, recent admission in intensive care unit) or other co-morbidities (hepatic and renal impairment), pregnant and lactating women, those taking drugs that may cause dysglycaemia (e.g. glucocorticoids) and those having other secondary causes of diabetes were excluded. Patients who gave informed written consent were interviewed and examined for relevant demographic and clinical information. A semi-structured data collection sheet was used to collect and record data which included general information on demographic characteristics, personal history of hypertension, family history of thyroid disease, diabetes, hypertension and dyslipidemia, and history of smoking, alcohol etc. Height, weight, waist circumference and blood pressure were measured by well-calibrated instruments, and body mass index (BMI) was calculated from height and weight. Obesity status was determined by body mass index (BMI) categories applicable to the Asian Indians and waist circumference ≥90 cm and ≥80 cm were used to define abdominal obesity for men and women respectively (12, 13). Hypertension was defined according to JNC VII criteria (14). All of the participants were asked to attend the OPD on another convenient day with overnight fasting for at least 8 hours and all attending patients underwent standard oral glucose tolerance test (OGTT) according to the procedure described by World Health Organization (15). Plasma glucose was assayed immediately by the glucose-oxidase method in the automated analyzer (Dade Behring, Germany). Normal glucose tolerance, prediabetes, and diabetes were diagnosed on the basis of the American Diabetes Association (ADA) criteria for the diagnosis of diabetes in non-pregnant adults (16).

Statistical analysis

Statistical analysis was done using Statistical Packages for Social Sciences (SPSS), version 23.0 software (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0, Armonk, NY: IBM Corp.). All data were expressed as mean±SD (or ±SE), median or in percentages as appropriate. Student's t-test or Chi-square test was used for comparison of the values of variables among different groups as applicable. Pearson correlation test was used to see correlation among different variables. Binary logistic regressions were used to see the influence of individual predictors on the presence of abnormal glucose tolerance (AGT). A p-value ≤0.05 was considered to be statistically significant.

Results

The demographic, clinical and biochemical characteristics of the study population and the comparison of those variables between subjects with normal glucose tolerance (NGT) and abnormal glucose tolerance (AGT) are shown in table 1. Subjects with AGT had higher mean age, higher frequency of family history of hypertension and diabetes, higher BMI, waist circumference, systolic blood pressure, TSH, FT4, and higher fasting and 2-hour post 75-gram OGTT values.

Table 1: Demographic, clinical and biochemical characteristics of the study population

Variables	Total Subjects (N=400)	Subjects with NGT (N=189)	Subjects with AGT (N=211)	*p*
Age (years, mean±SD)	37.21±11.65	36.68±12.27	38.58±10.92	0.013
Female Gender (%)	310 (77.5%)	147 (77.8%)	163 (77.3%)	0.905
Smoker (%)	37 (9.3%)	20 (10.6%)	17 (8.1%)	0.394
Family H/O Thyroid Disease Present (%)	54 (13.5%)	22 (11.6%)	32 (15.2%)	0.310
Family H/O DM Present (%)	156 (39.0%)	63(33.3%)	93 (44.1%)	0.031
Family H/O HTN Present (%)	169 (42.2%)	60 (31.1%)	109 (51.7%)	<0.001
Goiter Present (%)	322 (80.5%)	149 (78.8%)	173 (82.0%)	0.450
BMI (kg/m^2, mean±SD)	25.57±5.28	24.98±5.09	26.10±5.39	0.033
Waist Circumference (cm, mean±SD)	87.0±12.13	85.2±11.7	88.6±12.3	0.005
Systolic BP (mmHg, mean±SD)	125±14	122±13	128±15	<0.001
Diastolic BP (mmHg, mean±SD)	81±8	81±7	82±9	0.115
FPG	5.33±1.47	4.67±0.51	5.93±1.76	<0.001

(mmol/L, mean±SD)				
PG 2 hr after OGTT	8.26±3.09	6.14±0.95	10.16±3.12	<0.001
(mmol/L, mean±SD)				
S. TSH	23.83±1.98	28.1±3.1	20.0±2.5	0.041
(μIU/mL, mean±SEM)				
S. FT4	1.68±0.1	1.43±0.12	1.89±0.15	0.016
(ng/dL, mean±SEM)				

(within parentheses the percentage of the column total)

(p-value by Student's t-test or Chi-square test as applicable)

The glycemic status of the study population is given in table 2. 52.7% of the subjects had abnormal glucose tolerance (33.5% prediabetes and 19.3% diabetes). The frequency of NGT, prediabetes, and diabetes did not differ significantly among biochemically hypothyroid, hyperthyroid and euthyroid subjects with various thyroid disorders.

Table 2: Glycemic status of the study population

Glycemic Status	Total Subjects (N=400)	Hypothyroid Subjects (n=218)	Hyperthyroid Subjects (n=106)	Euthyroid Subjects (n=76)	p
NGT	189 (47.3%)	115 (52.8%)	41 (38.7%)	33 (43.4%)	0.055
AGT	211 (52.7%)	103 (47.2%)	65 (61.3%)	43 (56.6%)	
Prediabetes	134 (33.5%)	63 (28.9%)	48 (45.3%)	23 (30.3%)	
IFG	22 (5.5%)	8 (3.7%)	11 (10.4%)	3 (4.0%)	
IGT	86 (21.5%)	43 (19.7%)	29 (27.4%)	14 (18.4%)	
Both IFG & IGT	26 (6.5%)	12 (5.5%)	8 (7.5%)	6 (7.9%)	
Diabetes	77 (19.3%)	40 (18.3%)	17 (16.0%)	20 (26.3%)	

(within parentheses the percentage of the column total)

(p-value by Chi-square test)

The odds ratios calculated by binary logistic regression analysis of factors that may be related to abnormal glucose tolerance in the study population are given in table 3. Presence of family history of HTN and having abdominal obesity had the significant individual influence on the presence of dysglycaemia in the study population.

Table 3: Binary logistic regression for the predictors of dysglycaemia in study population

Variables	Subgroups	Odds Ratio (95% Confidence Interval)	p
Age group	<40 years	Reference	
	≥40 years	1.29 (0.784-1.924)	0.370
Gender	Female	Reference	
	Male	1.85 (0.942-3.634)	0.074
Years of schooling	≥10 years	Reference	
	<10 years	1.22 (0.763-1.937)	0.411
Smoking status	Non-smoker	Reference	
	Smoker	0.51 (0.208-1.272)	0.150
Family H/O thyroid disease	Absent	Reference	
	Present	0.91 (0.467-1.770)	0.780
Family H/O DM	Absent	Reference	
	Present	1.11 (0.641-1.909)	0.716
Family H/O HTN	Absent	Reference	
	Present	2.21 (1.302-3.746)	0.003
Goiter	Absent	Reference	
	Present	1.07 (0.588-1.932)	0.332
HTN	Absent	Reference	
	Present	1.86 (1.161-2.978)	0.332
BMI	<23	Reference	
	≥23	0.92 (0.472-1.775)	0.794
Abdominal obesity	Absent	Reference	
	Present	2.52 (1.285-4.930)	0.007
Thyroid functional status	Euthyroid	Reference	
	Thyrotoxic	1.83 (0.914-3.642)	0.088
	Hypothyroid	0.62 (0.344-1.135)	0.122

Discussion

DM and thyroid disease are closely linked. An array of complex intertwining biochemical, genetic, and hormonal malfunctions have been evidenced by many investigators mirroring this pathophysiological association (17). The observed frequency of dysglycemia in this study among the patients with thyroid disorders was 52.7%; of which 19.3% had DM and another 33.5% had prediabetes.

Several mechanisms have been described for dysglycemia in hyperthyroidism; the most important ones are, a) accelerated gastric emptying, enhanced intestinal glucose absorption and an increase in portal venous blood flow, b) increased insulin clearance, c) beta cell dysfunction resulting in reduced pancreatic insulin content, poor insulin response to glucose and decreased rate of insulin secretion, d) increased endogenous glucose production not responding to the suppressive effect of insulin, and e) exaggerated effects of glucagon and adrenaline on liver cells (2, 18, 19, 20). Though hypothyroidism predisposes to hypoglycemia, it may also cause insulin resistance (1). A higher degree of insulin resistance mainly at the peripheral muscles has been observed in overt and subclinical hypothyroidism in various in vitro and preclinical studies (5, 6, 7, 17). In contrast to this hypothesis of insulin resistance, some studies clearly demonstrated diminished early insulin secretory response to intravenous glucose in hypothyroid patients (8). These findings indicate that thyroid diseases play a role in the development of abnormal glucose tolerance.

Moreover, diabetes and hypothyroidism also meet each other through various common clinical characteristics; both are independently associated with changes in body weight, dyslipidemia, hypertension, and depression (1).

In the present study, the overall frequency of diabetes and prediabetes in patients with thyroidal illness were 19.3% and 33.5% respectively. These frequencies are higher than the national prevalence of diabetes (9.7%) and prediabetes (23%) of our country (21).

The frequency of diabetes in hypothyroid subjects in our study was 18.3% and that of prediabetes was 28.9%. In our scenario, the previous study done by Ashrafuzzaman et al. found a lower frequency of diabetes (7.01%) and prediabetes (21.2%, 12.6% IGT and 8.6 IFG) than us (22). The frequency of diabetes in hyperthyroid subjects in our study was 16% and that of prediabetes was 45.3%; in total 61.5% had dysglycemia. Paul et al. in their study found 72.3% of hyperthyroid patients to have glucose intolerance, which is higher than the frequency observed by us (23). Roubsanthisuk et al. found 39.4% (7.9% DM, 31.5% prediabetes) of Thai patients with hyperthyroidism to have dysglycemia (24). The higher frequencies of abnormal glucose tolerance in hypothyroidism in the current study may be due to small sample size, relatively higher mean age of study subjects and presence of other contributing factors such as increased waist circumference, and family history of diabetes.

The frequency of diabetes and prediabetes in our euthyroid subjects were 26.3% and 30.3% respectively. These patients had some forms of structural thyroid abnormality. There are very limited data regarding glucose intolerance in patients with simple diffuse or nontoxic nodular goiter and thyroid malignancy though some studies have found the relation between euthyroid goiter and insulin resistance (25, 26). Higher frequency of glucose intolerance in thyroid malignancy also has been reported by some authors (27).

Age is well-established risk factor glucose intolerance. Subjects with dysglycemia had higher age than those with NGT in our study although higher age (≥40 years) itself was not found to be a significant risk factor of dysglycemia in our study subjects. In contrast, Roubsanthisuk et al. found no significant different the mean age between the subjects with NGT and AGT (24).

Subjects with AGT had a higher frequency of family history of hypertension and had higher systolic BP in our study. Roubsanthisuk et al. had similar observations (24). Presence of family history of HTN and was associated with significantly higher odds of AGT; being hypertensive was also associated with higher risk of AGT though it was not statistically significant.

Though subjects with AGT had higher mean BMI, higher BMI (≥23 kg/m2) was not an individual risk factor of AGT in our study population. Roubsanthisuk et al. found no difference in BMI between AGT and NGT subjects in their study (24) Subjects with AGT had higher waist circumference and abdominal obesity imparted higher odds of AGT in them. Abdominal obesity is a marker of insulin resistance and thyroid dysfunctions are associated with insulin resistance.

Having hypothyroidism or hyperthyroidism was not associated with higher risks of AGT than euthyroid subjects in our study subjects though subjects with AGT had lower TSH and higher FT4 than subjects with NGT. Roubsanthisuk et al. found higher T4 in AGT subjects and Paul et al. observed a significant positive correlation between FT4 and plasma glucose in Graves' disease patients (23, 24).

Limitations of the study: The main limitation of this study is that had no healthy control group. It was a tertiary hospital-based single center study and the sample may not be representative to whole country. We did not measure HbA1c in our study subjects.

Conclusion

This study highlights the high frequency of diabetes and prediabetes among the newly detected subjects with thyroid disorders. There is no definitive guideline regarding screening of glucose intolerance for the patients with thyroid disorders. Findings of this study have evidenced the intricate bond between glucose intolerance and thyroid pathology. As South Asian ethnicity is an independent risk factor for type 2 diabetes mellitus, the additional presence of thyroid diseases should prompt the screening for glucose intolerance in our setting.

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