

Effect of Thyroid Dysfunction on Metabolic Response in Type 2 Diabetic Patients

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Received: 19 November, 2009 - Accepted: 26 January, 2010

ABSTRACT

OBJECTIVE: We aimed to evaluate association between thyroid dysfunction, and lipid profile and glycosylated hemoglobin in type 2 diabetic patients.

MATERIALS AND METHODS: This cross-sectional study was carried out in type 2 diabetic patients who referred to Yazd Diabetes Research Center. A total of 1200 type 2 diabetic patients who had thyroid dysfunction according to clinical examinations and laboratory results were chosen as case group and 1200 type 2 diabetic patients who were matched with case in age, sex and duration of diabetes and had no thyroid dysfunction confirmed by clinical and laboratory examination, were chosen as control group. In this study the following variables were measured: Glycosylated hemoglobin (HbA1c), lipid profiles [Total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG)].

RESULTS: There was a significant difference between HbA1c (8.9 ± 1.99 vs. 7.1 ± 1.02), TG (234.07 ± 88.69 vs. 205.89 ± 58.47), TC (209.56 ± 45.59 vs. 199.48 ± 41.55), LDL (125.05 ± 46.5 vs. 114.5 ± 45.42) and HDL (37.69 ± 16.78 vs. 43.79 ± 20.25) between two groups ($P = 0.001$). Moreover, a higher proportion of type 2 diabetic patients with thyroid dysfunction had elevated levels of TC (52.3% vs. 43.6%) ($P = 0.001$), LDL cholesterol (71.8% vs. 64.3%) ($P = 0.001$), HbA1c (83.8% vs. 35.9%) ($P = 0.001$) and TG (84.3% vs. 81.2%) ($P = 0.02$) compared with euthyroid group.

CONCLUSION: Our findings indicate that screening of thyroid dysfunction in type 2 diabetic patients is necessary because thyroid dysfunction can produce significant metabolic disturbances.

KEYWORDS: Type 2 diabetes mellitus, Thyroid dysfunction, Dislipidemia, Glycosylated hemoglobin.

INTRODUCTION

Diabetes mellitus and thyroid diseases are two common endocrinopathies seen in the adult population. Variable glucose intolerance is seen in up to 50% of patients with grave's disease (1). Long term thyrotoxicosis has been shown to cause beta cell dysfunction resulting in reduced pancreatic insulin content, poor

insulin response to glucose and decreased rate of insulin secretion (2). In hypothyroidism, the synthesis and release of insulin is decreased (3). The rate of hepatic glucose output is decreased probably due to reduced gluconeogenesis (4).

The physiological and biochemical interrelationship between insulin and the influence of both insulin and iodothyronines

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on the metabolism of carbohydrates, proteins and lipid have been recorded (5,6). Such records indicate that iodothyronines are insulin antagonist with high levels being diabetogenic while absence of the hormone inhibits the development of diabetes (6). Moreover, thyroid hormones have significant effects on the synthesis, mobilization and metabolism of lipids (7,8). Overt hypothyroidism is associated with significant increases in circulating concentrations of total and low density lipoprotein cholesterol (LDL-C) (9-11). Although there have been several large cross-sectional studies examining the association between thyroid dysfunction and metabolic abnormalities, few have studied type 2 diabetes. We aimed to evaluate association between thyroid dysfunction and, lipids and glycated hemoglobin in type 2 diabetic patients.

MATERIALS AND METHODS

This cross-sectional study was carried out in type 2 diabetic patients who referred to Yazd Diabetes Research Center from July 2006 to May 2008. The criteria for eligibility included type 2 diabetes according to ADA 2004 (12), fasting blood sugar of 126 mg/dl at more than one occasions, random blood sugar of 200 mg/dl in the presence of polyuria and polydipsia, taking hypoglycemic drugs or insulin, or physical exercise therapy for diabetes and not having any episodes of ketosis in the past, absence of severe diabetes complications and medical conditions that can affect thyroid function. Subjects with secondary diabetes and those who used medications that can affect thyroid function were excluded.

A total of 1200 type 2 diabetic patients, including new and review cases type 2 diabetes who had thyroid dysfunction according to clinical examinations and laboratory results and were not on therapy for thyroid dysfunction were chosen as case group and 1200 type 2 diabetic patients matched with case in age, sex and duration of diabetes who had no thyroid dysfunction confirmed by

clinical and laboratory examinations were chosen as control group.

The University Ethics Committee approval was obtained prior to study enrollment. Informed consent was obtained from all subjects and the presents of goiter were noted. Clinical data of all patients including sex, age at the onset of diabetes, duration of diabetes and thyroid diseases, as well as a history of thyroid dysfunction, were obtained by reviewing the medical records and direct patient interview.

Laboratory Assessment: Venous blood samples were collected after an overnight fasting, total cholesterol (TC), high-density lipoprotein (HDL) cholesterol, triglyceride (TG) and fasting blood glucose (FBS), as determined by enzymatic methods (PARS AZMON-Iran) and Glycosylated hemoglobin (HbA1c) was measured by HPLC method with DS5 analyzer. Low-density lipoprotein cholesterol was calculated by the Friedewald formula (13).

Sera were obtained from all patients for the measurement of thyroglobulin antibodies (TG-Ab) and thyroid peroxidase antibodies (TPO-Ab). TG-Ab and TPO-Ab were measured by enzyme-linked immunosorbent assay (ELISA) method (Radin Co., Italy). TSH, T3 and T4 were measured by radioimmunoassay (RIA) method (Kavoshyar Co., Iran). The normal range was TSH: 0.25–4.00 mU/l, T4: 4.5-11 ng/dl, T3:70-204 ng/dl, anti-TPO < 100 IU/ml and anti-TG <100 IU/ml.

A patient was labeled as hypothyroid if the TSH was more than 10 mU/l. Subclinical hypothyroidism was defined as a normal free T4 in association with a raised TSH (3-10 mU/l) in subjects not on thyroxin therapy. Hyperthyroidism was considered if TSH was less than normal range.

Statistical Analysis: Statistical analyses were performed using SPSS for windows, version 13. Data are presented as mean \pm SD. Student T-test, ANOVA and chi-square were used for analysis. A significant level of $P < 0.05$ was used for univariate test.

RESULTS

Of 1200 patients with thyroid dysfunction, frequency of thyroid disorders was as follows: hyperthyroidism 167 (7%), subclinical hypothyroidism 396 (16.5%), hypothyroidism 637(26.5%). Of patients studied, 22 were less than 35 years, 118 were 35-44 years, 653 were 45-54 years, 847 were 55-64 years, 642 subjects were 65-74 years and 118 were more than 74 years.

Mean serum lipids and HbA1c are presented according to diseases state in Table 1.

There was a significant difference between HbA1c (8.9 ± 1.99 vs. 7.1 ± 1.02), TG (234.07

± 88.69 vs. 205.89 ± 58.47), TC (209.56 ± 45.59 vs. 199.48 ± 41.55), LDL (125.05 ± 46.5 vs. 114.5 ± 45.42) and HDL (37.69 ± 16.78 vs. 43.79 ± 20.25) between two groups ($P = 0.001$). Moreover, a higher proportion of type 2 diabetic patients with thyroid dysfunction had elevated levels of TC (52.3% vs. 43.6%) ($P = 0.001$), LDL cholesterol (71.8% vs. 64.3%) ($P = 0.001$), HbA1c (83.8% vs. 35.9%) ($P = 0.001$) and TG (84.3% vs. 81.2%) ($P = 0.02$) compared with euthyroid group. Frequency of HDL cholesterol more than 40 mg/dl was higher in euthyroid group compared with subjects with thyroid dysfunction (35.7% vs. 28.3%) ($P = 0.001$).

Table 1- Mean serum lipids and HbA1c levels according to diseases state in subjects studied

Type of disease	Gender	Hyperthyroidism	Overt hypothyroidism	Subclinical Hypothyroidism	Euthyroidism	P value
HbA1c (%)	Male	9.07 ± 2.05	9.01 ± 2.06	9.03 ± 1.99	7.11 ± 0.99	0.68
	female	9.07 ± 2.11	9 ± 1.94	8.81 ± 2	7.19 ± 1.04	
TG (mg/dl)	Male	236.79 ± 79.72	213.46 ± 83.2	246.9 ± 107.82	203.39 ± 58.85	0.15
	female	237.34 ± 79.35	225.48 ± 76.65	225.29 ± 100.81	207.16 ± 58.27	
TC (mg/dl)	Male	219.23 ± 48.91	201.08 ± 35.47	210.31 ± 48.55	195.26 ± 39.04	0.03
	female	217.57 ± 50.65	202.73 ± 41.46	221.6 ± 51.11	201.62 ± 42.63	
LDL (mg/dl)	Male	126.72 ± 51.95	122.32 ± 34.41	125.52 ± 56.78	109.85 ± 44.04	0.05
	female	124.91 ± 48.38	120.36 ± 38.78	134.53 ± 55.85	116.87 ± 45.95	
HDL (mg/dl)	Male	45.15 ± 27.64	36.06 ± 11.12	35.4 ± 12.89	44.73 ± 23.89	0.37
	female	45.18 ± 18.39	37.27 ± 16.17	36.01 ± 16.37	43.32 ± 18.13	
P value		0.001	0.001	0.001	0.001	

Table 2- Comparison of elevated levels of Lipids and HbA1c in patients with thyroid dysfunction and control group

		Thyroid dysfunction	Euthyroid	OR
HbA1c (%)	≥ 7	1021 (85.1%)	641 (53.4%)	0.11 (CI: 0.09-0.13)
	< 7	179 (14.9%)	559 (46.6%)	
TG	≥ 150	1015 (84.6%)	980 (81.7%)	0.74 (CI:0.58-0.95)
	< 150	185 (15.4%)	220 (18.3%)	
LDL	≥ 100	865 (72.1%)	777 (64.8%)	0.86 (CI:0.7-1.05)
	<100	335 (27.9%)	423 (35.3%)	
HDL	≤ 40	913(76.1%)	764 (63.7%)	0.59 (CI:0.48-0.72)
	> 40	287 (23.9%)	436 (36.3%)	
TC	≥ 200	670 (55.8%)	568 (47.3%)	0.7 (CI:0.6-0.82)
	< 200	530 (44.2%)	632 (52.7%)	

In all subjects studied, mean serum TG and HbA1c concentration varied significantly with increasing TSH levels ($P = 0.001$), but serum TC and LDL cholesterol did not change significantly (Figure 1).

Frequency of elevated HbA1c (60.2% vs. 9.9%), TG (43.5% vs. 7.4%) and LDL levels (45.7% vs. 7%) among patients with hypothyroidism was significantly higher than elevated levels in hyperthyroid subjects ($P = 0.001$).

There was a significant positive correlation between T4 and, HDL ($r = 0.08$, $P = 0.001$), TG ($r = 0.04$, $P = 0.04$), and TC ($r = 0.04$, $P = 0.01$) and negative correlation between T4 and HbA1c ($r = -0.05$, $P = 0.004$). There was a positive correlation between TSH and, HbA1c ($r = 0.2$, $P = 0.001$) and TG ($r = 0.04$, $P = 0.05$), and a negative correlation between TSH and HDL (-0.11 , $P = 0.001$). A positive correlation was found between age and HbA1c ($r = 0.05$, $P = 0.004$) and HDL ($r = 0.03$, $P = 0.05$), but there was no significant correlation between age and other variables.

Although mean TSH increased with age until 54 years, but this variation was not significant ($P = 0.09$).

Across the groups, the majority of patients with thyroid dysfunction had coexistent TPO-Ab (73% vs. 35%) ($P = 0.001$), but it was not true about TG-Ab and thyroid dysfunction (41.3% vs. 58.7%) ($P = 0.001$).

DISCUSSION

Among 1200 type 2 diabetic patients with thyroid dysfunction, 167 (7%) had hyperthyroidism, 637 (26.5%) had overt hypothyroidism, and 396 (16.5%) had subclinical hypothyroidism.

The type 2 diabetic subjects with thyroid dysfunction tended to have higher levels of blood lipids and HbA1c compared with those of control. This confirms that thyroid hormones affect on blood glucose as well as lipid levels or vice versa. As Bagchi et al. showed that the thyroidal secretory response to large doses of TSH is decreased in uncontrolled type 2 diabetes mellitus and strict glycemia control

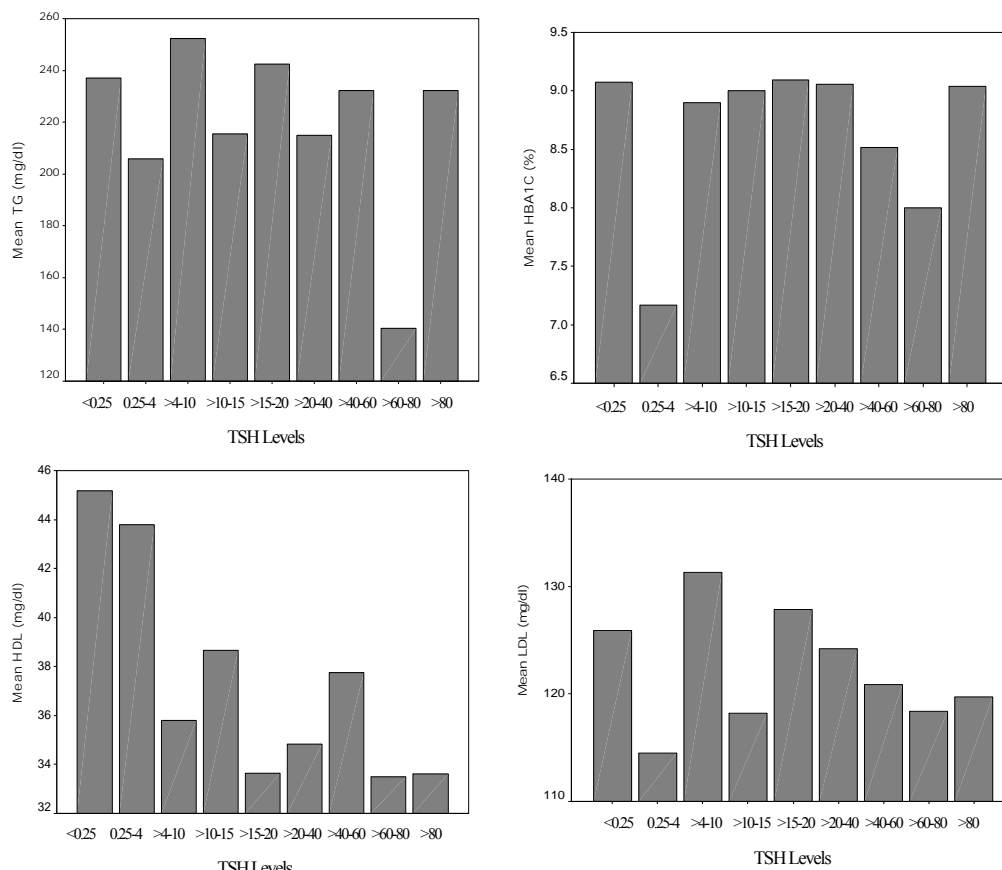


Figure 1- The levels of lipids and HbA1c according to TSH levels

improves the response (14). Also in Castro's study, patients showed significantly lower serum T3 levels and significantly higher serum rT3 levels in comparison with a group of normoglycemic subjects. In this study after 3 months treatment, these patients showed significant decrease of rT3 and delta-TSH. They concluded there is a connection between alternations in thyroid hormone picture and glycometabolic imbalance (15).

It may be due to this hypothesis that the bulk of the hormones secreted by follicular cells of the thyroid gland are released in the free form into plasma where it becomes largely bound to thyroid binding globulin (TBG) and to some extent to pre-albumin and albumin. A small fraction circulates free in plasma (free T4, FT4) (16). Suzuki et al. attributed the abnormal thyroid hormone levels found in diabetes to the presence of Thyroid Hormone Binding Inhibitor (THBI), an inhibitor of extra thyroidal conversion enzyme of T4 to T3, and dysfunction of the hypothalamus-hypophyseal-thyroid-axis (17). These situations may prevail in diabetics and would be aggravated in poorly controlled diabetics. Stress, which is associated with diabetes mellitus, may also cause changes in the hypothalamus anterior-pituitary axis in these diabetics. It appears that the presence of subclinical hypothyroidism and hyperthyroidism may result from hypothalamus-hypophyseal-thyroid axis disorders as suggested by Celani et al. (18). Suggestion was made that the confirmed cases of hypothyroidism or hyperthyroidism receive adequate attention and proper treatment (19).

Dyslipidemia is a reported complication of overt hypothyroidism in non-diabetic (9,10,20) and diabetic (21) subjects. In our study serum lipids and HbA1c were significantly higher and HDL was lower in subjects with subclinical hypothyroidism compared with age and sex matched euthyroid subjects. This result is consistent with some previous studies (22-25). Nevertheless some studies could not show this difference significantly (26-30). Even in one study lipid levels were higher in euthyroid subjects (31).

The trend across thyroid dysfunction states for mean TC, LDL cholesterol and TG were statistically significant. This finding is consistent with that of Colorado thyroid study (24).

Several studies have linked hyperlipidemia with cardiovascular morbidity (32-34). So thyroid function may have a role in the treatment of hyperlipidemia and can prevent associated cardiovascular morbidity.

A higher mean TC and LDL were found in hyperthyroid subjects in this study. This observation disagrees with some studies in diabetic patients (35) and general non-diabetic population (10,36).

Our findings showed not only elevations of TSH levels but also decline of TSH could change lipid levels and might affect cardiovascular outcome in type 2 diabetic patients.

The mean serum TSH increased progressively with age in thyroid dysfunction group until 55 and after that it decreased. Nevertheless, results of large community study, (37) showed that after all subjects with thyroid dysfunction and thyroid risk factors were excluded, the mean serum TSH rose progressively with increasing age.

Population screening for thyroid dysfunction may prevent the development of overt thyroid function and may allow early treatment of hyperlipidemia (30,38), control of glycemia and prevention of associated cardiovascular complications (31). Accordingly, screening for thyroid dysfunction should be considered in type 2 diabetic patients especially in patients aged 45-54 years.

CONCLUSION

Our findings indicate that screening of thyroid dysfunction in type 2 diabetic patients is necessary because thyroid dysfunction can produce significant metabolic disturbance.

ACKNOWLEDGMENTS

This study was supported by Yazd Diabetes Research Center of Shahid Sadoughi University of Medical Sciences.

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