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Original Article

Thyroid Function in Euthyroid Subjects and Its Association with Insulin Resistance

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ABSTRACT

Background: Diabetes mellitus [DM] and thyroid dysfunction are the most commonly coexistent disorders. Hypo- and hyperthyroidism are causes of dysglycemia. However, the relation between normal thyroid hormone levels and insulin resistance [IR] is unclear.

The aim of the work: This study aimed to examine the association between the normal values of thyroid hormones and glucose metabolism and to investigate whether improvement of metabolic status can restore thyroid function in patients with uncontrolled type-2 diabetes mellitus [T2DM].

Patients and Methods: This study was a retrospective observational study. A total of 120 euthyroid participants were recruited. They were classified into four groups: Normal glucose tolerance [NGT, n =28], Prediabetes [n=32], well controlled DM [T2DM with glycated hemoglobin [HbA1c] ≤ 7%, n =26], and uncontrolled DM [T2DM with HbA1c > 7%, n = 34]. The results were compared between groups and the changes before and after treatment in uncontrolled DM group were observed and documented.

Results: A total sample of 120 participants showed that mean age of DM uncontrolled patients was 40.2± 19.5 and there were no significant differences among groups regarding their age, body mass index [BMI], blood pressure [BP]. However, groups showed significant differences regarding cholesterol, free t_4, serum glucose, two hours post prandial glucose, HbA1c, fasting insulin and insulin resistance. Regression analysis revealed that BMI, HbA1C, low density lipoprotein [LDL], triglycerides [TG] and total thyroxine [TT_4] had statistically significant association with insulin resistance. there is statistically significant difference between uncontrolled DM patients before and after treatment regarding HbA1C and glucose.

Conclusion: Reduced levels of free thyroid hormones [although in normal range] were significantly associated with high levels of serum glucose and HOMA-IR. There was significant improvement of blood glucose levels and insulin resistance.

Keywords: Metabolic Diseases; Thyroid Hormone; Blood Glucose; Insulin Resistance.

INTRODUCTION

Insulin resistance [IR] is a glucose homeostasis disorder included a reduced sensitivity of differ organs [e.g, muscles, liver, and adipose tissues to insulin]. It is a hallmark character of type-2 diabetes mellitus [DM] [1]. Thyroid hormones are very important in regulation of energy balance, and in the metabolism of different foods [e.g., carbohydrates and lipids]. In patients with DM, the incidence of different thyroids disorders is much more common than in normal healthy subjects. Thus, a possible link

between both conditions and the relation between insulin sensitivity and thyroid hormone levels could be anticipated [2].

The action of thyroid hormones on insulin could be agonistic or antagonistic in different tissues. One study suggested that, thyroid hormone exerts a role in the development of insulin resistance through different and complex mechanisms [e.g., bio-chemical, genetic and secretory mechanisms]. Thyroid dysfunction also associated with the development of metabolic syndrome and the development of cardiovascular disease [CVD] [3]. However, some actions are paradoxical. For example, hyperthyroidism is associated with IR. However, hypothyroidism was reported to be associated with IR in a previous study [4]. In addition, a more recent study revealed that, low and low-normal thyroid hormones were risk factors for DM [5]. Another study revealed that higher thyroid stimulating hormone [TSH] levels were linked to a higher risk of DM, even in patients with a normal function of the thyroid gland. In addition, high levels of free thyroxine [FT4] were associated with a reduced DM risk in abnormal as well as normal thyroid function [6].

In addition, during different stages of impaired glucose regulation as associated with variable thyroid hormone levels. Also, patients with T2DM had lower levels of thyroid hormones than subjects with normal glucose tolerance [NGT]. In prior research on prediabetes, researchers reported that free T_3 was negatively correlated with the risk of impaired glucose tolerance [IGT], while free T4 was positively correlated with the risk of impaired glucose tolerance [7]. However, few previous reports had examined the levels of thyroid hormones in euthyroid conditions in relation to the regulation degree of glucose intolerance. Meanwhile, the effect of improved metabolic indicators, on the function of the thyroid gland remains largely unclear [8,9].

Serum levels of TSH were positively correlated with elevated glucose levels [hyperglycemia] and IR in subjects with normal thyroid function in different studies. TSH may directly affect metabolism of different substances and induce the secretion of leptin in fatty tissues. It exerts a crucial role in the metabolism of glucose in the liver with stimulation of hepatic production of glucose. Moreover, TSH decreases secretion and synthesis of insulin and subsequently increases the values of serum blood glucose [10].

The interaction between thyroid hormones, β cell function, hepatic metabolism of glucose, intestinal absorption of sugar, and lipids metabolism is complex and not clearly understood. Interestingly, IR is associated with both hypo- and hyper-thyroidism [11]. On the other side, present evidence suggested that impaired glucose tolerance associated with hyper-thyroidism is primarily the outcome of hepatic IR [12].

THE AIM OF THE WORK

This study aimed to investigate the association of the thyroid hormone levels [within the normal range] and the serum glucose levels and IR. In addition to examine whether the improvement of metabolic status could reestablish the thyroid function in uncontrolled T2DM.

PATIENTS AND METHODS

Study participants: We evaluated data of 120 participants with [n=60] or without [n=60] type-2 diabetes mellitus. They were selected from the department of internal medicine and outpatient clinic, Al-Azhar University Hospitals, Egypt, from September 2018 to August 2020. Oral glucose tolerance test [OGTT] for participants with preexisting DM was carried out.

The following were excluded: [a] those with infection, chronic disease [e.g., liver disease, or renal disease]; [b] patients with type 1 diabetes [T1D]; [c] those with a history of thyroid disease or receiving thyroid-related drugs; and [d] patients with abnormal thyroid function [abnormal levels of T3 or T4, thyroid stimulating hormone [TSH], anti-thyro-globulin and thyroid peroxidase antibody levels].

After exclusion, 120 subjects were included and evaluated. Then they were divided based on the results of oral glucose tolerance test: normal glucose tolerance [NGT] [n=28], prediabetes [n=32], well controlled type-2 DM [T2DM; HbA1c ≤ 7%, n=26], and uncontrolled DM [HbA1c > 7%, n=34]. The definition of these categories based on the World Health Organization [WHO] guidelines [13]. NGT was identified as serum fasting glucose <6.1 mmol/L [110mg/dl] and 2-hours OGTT serum glucose <7.8 mmol/L [140g/dl]; prediabetes was recognized as serum fasting glucose ≥6.1 mmol/L [110mg/dl] and <7.0 mmol/L [126g/dl] and/or 2-hours OGTT serum glucose levels ≥7.8 mmol/L [140g/dl] and <11.1 mmol/L [200g/dl]; and T2DM was recognized at the fasting serum glucose level ≥7.0 mmol/L [126g/dl], and/or 2 hours OGTT serum glucose ≥11.1 mmol/L [200g/dl], or the patient on the blood glucose-lowering drugs.

Ethical considerations: A written informed consent was signed by each participant before inclusion. The study protocol was examined and accepted by the local research ethics committee of Damietta Faculty of Medicine, Al-Azhar University, Egypt [IRB 00012367-18-09-004]. The research was completed in line with declaration of Helsinki research ethics.

Management of T2DM

T2DM management protocol at our department depend on a management model arise from an internet health information platform. It is usually one step protocol with a series of services [registration, clinical and laboratory evaluation, prescriptions, health education and a uniform follow up protocol of care] [14]. Anthropometric measurement, hemo-dynamics, serum blood glucose level, glycated hemoglobin, liver and kidney function were determined every 3 months. The function of islet function, thyroid function and diabetic complications were evaluated on a yearly basis.

Data collection and laboratory measurements

The history and sociodemographic data of each patient were collected and document by a trained staff. Anthropometry were completed using standard instruments. Blood pressure was measured with sphygmomanometer. For oral glucose tolerance test, blood samples to measure glucose and insulin were obtained from the antecubital vein and samples were collected at 0 and 120 minutes after carbohydrate or glucose loading. Liver enzymes, kidney function tests, and lipid profiles were assessed by an automatic biochemistry analyzer. Immunochemi-luminescence was used to measure fasting and postprandial insulin, and HOMA-IR was calculated. Electrochemiluminescence analyzer with mating reagents were used to estimate free T3, T4, TSH, reverse T3, and antithyroid autoantibodies. BMI was estimated through calculation from the equation: [BMI= weight [kg]/height squared [m^2]]. Hypertension was defined as a blood pressure greater than 140/90 mmHg [or patients were on antihypertensive drug therapy] [15].

Statistical analyses

Statistical analysis was completed by the SPSS for Windows [version 20.0; IBM®SPSS®, Chicago, IL, USA]. Continuous normally distributed variables were presented by their arithmetic mean± standard deviation [SD]; while data with abnormal distribution were presented by median and their [interquartile range]. Qualitative variables are presented as relative frequency and [percentages]. Comparisons between more than two means was done by one-way analysis of variance [ANOVA]. To evaluate the effect of management of uncontrolled diabetes group, paired sample "*t*" test was used. HOMA-IR values were transformed to their log values to be better fit in the linear regression models. Linear regression analyses were done to estimate linear correlations between variables. *P* values < 0.05 were considered significant.

RESULTS

As shown in table [1], there was no significant difference between studied groups regarding mean age, body mass index and blood pressure [systolic and diastolic values].

In the current work, there was significant difference between groups regarding total cholesterol. The highest value was registered in the NGT group [216.4± 64.9], while the lowest values were registered in uncontrolled DM group [196.1± 78.4]. In addition, there was significant differences between groups regarding free T4, being highest among prediabetes, glucose, and 2 hours postprandial sugar, fasting insulin, HOMA-IR and fasting insulin. However, no significant differences were observed regarding triglycerides, HDL-cholesterol, LDL-cholesterol and thyroid stimulating hormone [Table 2].

Multiple linear regression showed that BMI, HbA1C, LDL, TG and TT_4 had were significantly association with insulin resistance [Table 3]. Table 4 showed that there is statistically significant difference between uncontrolled DM patients before and after treatment regarding HbA1C and Glucose [fasting and 2 hours postprandial values].

Table [1]: General characteristics among groups

Variables	NGT	Prediabetes	DM well-controlled	DM uncontrolled	p-value
Age [years]	39.8± 13.7	37.4± 11.6	35.0± 14.1	40.2± 19.5	0.924
BMI [kg/m^2]	28.1± 4.5	29.9± 3.8	24.9±1.8	25.4± 2.7	0.104
SBP [mmHg]	128.5± 11.7	131.4± 9.3	125.8± 7.5	130.4± 12.1	0.085
DBP [mmHg]	79.4± 9.8	81.3± 5.5	80.9± 9.7	82.1± 8.4	0.130

BMI: Body mass index; NGT: normal glucose tolerance; SBP systolic blood pressure; DBP diastolic blood pressure; DM: Diabetes mellitus; data presented as mean ± SD [standard deviation].

Table [2]: Metabolic parameters and difference among groups

Variables	NGT	Prediabetes	Well-controlled DM	Uncontrolled DM	P-value
TC [mg/dl]	216.4± 64.9	206.1± 85.2	189.3± 69.7	196.1± 78.4	**0.041***
TG [mg/dl]	128.6± 62.3	121.6± 51.2	134.8± 59.4	142.5± 48.6	0.215
HDL-C [mg/dl]	56.5± 13.2	49.3± 11.8	46.7± 10.9	53.4± 14.3	0.061
LDL-C [mg/dl]	91.1± 19.3	93.5± 23.7	87.3± 25.7	95.4± 20.1	0.650
TSH [mUI/I]	1.5± 0.7	1.9± 0.5	2.7± 0.9	3.9± 1.2	0.244
FT_4 [PmoI/I]	13.2± 2.7	14.5± 1.9	13.9± 1.3	12.4± 2.8	**0.005***
Glucose [mg/dl]	92.2± 1.2	90.5± 0.7	105.1± 5.2	130.4± 8.7	**<0.001***
2hour- glucose [mg/dl]	98.1± 4.2	95.3± 3.6	120.2± 6.7	155.3± 8.1	**0.002***
HbA1C	4.1± 0.7	4.9± 0.6	6.3± 0.9	9.8± 1.7	**0.032***
FINS [mUI/I]	17.4± 13.9	17.4± 13.9	17.4± 13.9	17.4± 13.9	**<0.001***
HOMA-IR	2.5± 1.4	2.9± 0.3	3.2± 1.1	3.5± 1.6	**0.001***

TCL Total cholesterol; TG: triglyceride; HDL-C: high density lipoprotein cholesterol; LDL: low density lipoprotein cholesterol; TSH: thyroid stimulating hormone; FINS: fasting serum insulin; HOMA-IR: homeostasis model of assessment insulin resistance; *p is significant at < 0.05, one way analysis of variance was to assess the difference between means.

Table [3]: Multiple linear regression analysis associated with insulin resistance

Variables	Unstandardized		Standardized	t	P value
	β	SD	*β*		
BMI	0.142	0.069	0.110	2.047	**0.041***
HbA1C	1.097	0.130	0.981	8.452	**<0.001***
LDL	1.398	0.521	1.587	2.683	**0.007***
HDL	0.592	0.543	0.927	1.089	0.276
TG	0.555	0.175	1.102	3.170	**0.002***
TT3	-0.293	0.287	-0.054	-1.022	0.307
TT4	0.018	0.006	0.136	2.997	**0.003***
TSH	0.028	0.026	0.141	1.070	0.285

*P is significant at <0.05; BMI: Body mass index, HbA1C: Glycated hemoglobin; LDL: Low density lipoprotein; HDL: High density lipoprotein; TG: Triglycerides; TT3: Total Thyroxin; TT4: total thyroxin-4; TSH: Thyroid stimulating hormone.

Table [4]: Effect of treatment in uncontrol DM group

Variables	Before treatment	After treatment	*P value*
HbA1C	9.8± 1.7	6.5± 1.2	**<0.001***
Glucose	130.4± 8.7	124.6± 6.3	**0.004***
2 hour-glucose	155.3± 8.1	133.9± 9.2	**0.002***
FINS	17.4± 13.9	15.5± 11.8	0.411

Paired t-test was used to assess difference; FINS: Fasting serum insulin; HbA1C: Glycated hemoglobin; *: Significant

DISCUSSION

Type 2 DM is a global health problem, with insulin resistance [IR] as a hallmark of the disease, with reduced secretory function of pancreatic beta cells. The association between DM and minerals has been well recognized. DM is a chronic disorder of glucose metabolism. It is high prevalent worldwide and has a major impact on the patient's QoL [16,17].

Thyroid hormones were identified as catabolic hormones and regulated many metabolic processes, including lipid synthesis, mobilization and break-down. Hypothyroidism had been associated with a high dyslipidemia and atherosclerosis risk, with increased cardiovascular morbidities [18].

In terms of insulin resistance [IR] evaluation, most of the prior studies evaluated IR using HOMA-IR [19].

In this study, we intended to investigate the link of thyroid hormones [within normal range] with the metabolism of glucose and IR and to explore whether improvement of metabolic status of diabetes could reestablish thyroid function in uncontrolled T2DM.

Results demonstrated that there was significant difference between our four groups regarding total cholesterol, T_4, glucose levels, insulin and glycated hemoglobin. Insulin resistance was associated with body mass index, HbA1C and LDL-C. Also, there were no association between insulin resistance and T3 and TSH. However, T_4 was significantly associated with IR and this finding consistent with a study conducted to evaluate the associations between thyroid hormone levels, body mass index and IR in subjects with normal values of thyroid hormones and normal thyroid US findings [20].

In addition, total T_4 levels exhibited positive associations with HOMA-IR and a negative association with body weight and BMI after adjustment for age, SBP, DBP, TG, HDL, LDL and glucose among both males and females [21].

Free T3, the active form of thyroid hormone, binds to the nuclear thyroid hormone receptors inside the nucleus. Increased serum free T3 levels be due to changes in the monodeiodination metabolic pathway [22].

About 80% of serum levels of free T3 is formed by extrathyroidal T3 monodeiodination, whereas reserve T3 [rT3] is mainly produced by extra-thyroidal monodeiodination of T4. It is well documented that insulin and T3 reciprocally control the rate of glycolysis and storage of glucose at the molecular as well as at the physiological levels [23].

In a study conducted to determine the potential link between IR and thyroid hormones in a population of healthy individuals, Wang *et al.* [2] reported an association between free T3 tertiles and IR and significant association between BMI and IR. However, they did not find any significant correlation between free T4 tertiles and IR.

The association between free T3 and IR had been also reported in a Turkish study included 211 subjects [187 women and 24 men] with a mean age of 39.7±11.7 years, who had negative history for previous hormonal abnormalities and their mean BMI was ≥30 kg/m^2. Authors found that high levels of freeT3 and T4 were significantly correlated with IR. However, all patients in their study were obese. Obesity is known to affect thyroid function and considered as a primary risk factor for IR. Therefore, obesity and overweight might affect the reliability of results [24].

Another trial found a statistically significant link between thyroid hormones and metabolic variables in obese women with polycystic ovarian syndrome [PCOS]; the association that disappeared in non-obese PCOS subjects.

These results refer to the significant role of body weight in modulation of the link between metabolic features and thyroid function [25].

In the current work, there was no significant link between IR and TSH. However, another study conducted by Liu *et al.* [26] showed that serum TSH had a positive association with HOMA-IR. High IR was positively correlated with serum free T3 values, and inversely correlated with serum TSH values in euthyroid participants with normal US of the thyroid gland.

Laclaustra *et al.* [27] demonstrated that at low insulin sensitivity relatively minor differences in TSH are lined to marked changes in lipid levels, a risk factor for cardiovascular disease.

According to results of the current study, IR was higher in diabetic [well-controlled and uncontrolled] participants than others [NGT and preexisting diabetes].

A previous work by Benites-Zapata *et al.* [28] showed that impaired glucose tolerance subjects had hyperinsulinemia and IR.

It is crucial to note that prior trials have identified many issues regarding the significant positive correlation between serum levels of TSH and insulin resistance and positive correlations between IR and free T4 and T3 [18,20,26].

Others reported complete opposite results, such as a negative correlation between TSH, free T4, free T3, and IR [20; 26,27, 29].

Most of trials found that, only one hormone was significantly associated with insulin resistance, some found an association with both hormones, and several studies found no correlation [22, 30 ,31].

Our results could not provide a final clue for the debate. Thus, the association between thyroid hormones in euthyroid subjects and insulin resistance remains unclear and needs further evaluation. However, the fact that, thyroid function

could affect insulin sensitivity could not be excluded.

The limitations of the current work: The abnormal increase of body weight might influence thyroid hormone levels, in a reciprocal action. Some of our patients were obese. Another limitation was the use of the HOMA-IR mathematical model to calculate insulin resistance [IR] instead of the "Hyperinsulinemic-euglycemic Clamp Method", which is the gold standard for the diagnosis of diabetes. However previous studies have shown a very high correlation between the two values.

Conclusion:

Our results indicated that elevated T4, body mass index and LDL-C are related to abnormal glycemic levels and insulin resistance. We suggested that elevation of these factors indicate involvement of thyroid gland in insulin resistance.

Financial and non-financial activities and relations of interest

Authors declare that there was no conflict of interest. The research funded by the researchers themselves.

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