Elmer Press

Original Article

J Endocrinol Metab. 2015;5(1-2):179-183

Thyroid Hormones Protect Type 2 Diabetes Obese Patients Against Cardio-Metabolic Risk Factors

Zhian M. I. Dezayee[a], Marwan S. M. Al-Nimer[b, c]

Abstract

Background: Dysfunction of thyroid gland was observed in obese and type 2 diabetes (T2D) patients. The serum level of thyroid stimulating hormone (TSH) is increased in these conditions and inversely correlated with risk factors that related to cardiovascular events. This study aimed to demonstrate the changes in the serum level of thyroid hormones; triiodothyronine (T3) and thyroxin (T4) and TSH in obese T2D patients and to demonstrate the gender-based effect of these hormones against the cardio-metabolic risk factors that existed in those patients.

Methods: A total number of 150 obese T2D patients (100 women and 50 men) recruited from Martyr LaylaQasm Center for Diabetes Mellitus in Erbil, Iraq during 2013 were enrolled in this study. The cardio-metabolic risk factors are assessed via measuring body weight, body mass index (BMI), waist circumference, blood pressure, fasting serum glucose and lipid profile, glycosylated hemoglobin and high sensitive C-reactive protein (hsCRP). Serum total T4, T3 and TSH were measured.

Results: The serum levels of T4 and T3 attended higher levels in women compared with men while the TSH level is less in women than in men. The significant positive correlations between the TSH and the cardio-metabolic risk factors (except fasting serum glucose and hsCRP) were observed. An inverse pattern was observed with T4 and T3. The coefficient factors of these correlations were higher in women compared with men.

Conclusions: It concludes that the thyroid gland function is disturbed in obese T2D patients, and thyroid hormones were significantly and inversely correlated with cardio-metabolic risk factors which were prominently observed in men.

Manuscript accepted for publication April 13, 2015

[a]Department of Microbiology, Hawler University, Erbil, Iraq
[b]Department of Pharmacology, College of Medicine, Al-Mustansiriya University, PO Box 14132, Baghdad, Iraq
[c]Corresponding Author: Marwan S. M. Al-Nimer, Department of Pharmacology, College of Medicine, Al-Mustansiriya University, PO Box 14132, Baghdad, Iraq. Email: alnimermarwan@ymail.com

doi: http://dx.doi.org/10.14740/jem274w

Keywords: Obesity; Type 2 diabetes; Thyroid hormones; Cardio-metabolic factors

Introduction

The obesity is considered as a risk factor of cardiovascular events and dysfunction of thyroid gland is observed in obese patients. An inverse linear association of anthropometric measurements including waist circumference and body mass index (BMI) with serum thyroid stimulating hormone (TSH) levels was observed in adult [1]. In young women, the higher prevalence of metabolic syndrome was reported significantly in those with a TSH level > 2.5 mIU/L and they had a two-fold greater risk of metabolic syndrome [2].

In obese children, the serum levels of TSH and free triiodothyronine (fT3) were higher than non-obese, and the TSH was positively correlated with total cholesterol (TC), triglycerides (TG), and systolic blood pressure [3]. Another study observed a significant association between TSH levels and impaired fasting glucose, impaired glucose tolerance, high TC, high low-density lipoprotein cholesterol (LDL-c) and high TG [4].

In women, there is a relation between the metabolic syndrome components with TSH and fT3 levels irrespective of the menopausal status [5]. Moreover, non-diabetic non-obese patients who presented with low thyroid function (even in the euthyroid state) were predisposed to have high cholesterol, glucose, insulin, and insulin resistance levels [6].

In T2D, there is non-significant difference between patients with euthyroid and subclinical hypothyroidism in term of serum TG or high-density lipoprotein-cholesterol (HDL-c) and TSH level does not show significant correlation with these parameters [7]. Thyroid dysfunction was reported in diabetes and the hormonal profile showed subclinical or overt hypothyroidism and the level of TSH reduced with oral hypoglycemic agents particularly metformin [8]. Wang et al demonstrated a significant association between acute insulin responses (using arginine stimulating test) withT3 and fT3 indicated the protective effect of thyroid hormones for beta cell function in T2D [9]. There is evidence that the changes in thyroid function (increase TSH and fT4) are related to the adiposity and insulin resistance that present in obese or T2D patients [10]. Further

Table 1. Characteristics of the Patients

Variables	Women (n = 100)	Men (n = 50)	P value
Age (year)	51.5 ± 4.3 (50)	52.4 ± 4.6 (50)	0.237
Family history of diabetes	24 (24)	16 (32)	0.296
Duration of diabetes (year)	3.15 ± 1.60 (3)	3.02 ± 1.48 (3)	0.622
Weight (kg)	97.5 ± 9 (94.5)	92.7 ± 10.3 (89)	0.006*
Height (m)	1.63 ± 0.045 (1.62)	1.62 ± 0.039 (1.61)	0.165
Body mass index (kg/m^2)	36.57 ± 2.15 (36.73)	35.16 ± 2.54 (34.33)	0.001*
Waist circumference (cm)	90.34 ± 7.4 (87.5)	88.3 ± 8.4 (86)	0.147
Waist/height ratio	0.553 ± 0.036 (0.55)	0.554 ± 0.042 (0.525)	0.178

*Significant. The results are expressed as number (%) and mean ± SD (median).

study showed that the components of metabolic syndrome (except HDL-c) correlated with T3 (independent to the insulin resistance) and free T4 (in the presence of insulin resistance status) [11].

This study aimed to demonstrate the gender-based effect of thyroid hormones as well as TSH against the cardio-metabolic risk factors that observed in obese T2D.

Materials and Methods

This cross-sectional study was conducted in Martyr LaylaQasm Center for Diabetes Mellitus in Erbil, Iraq in cooperation with Department of Pharmacology, College of Medicine at Al-Mustansiriya University in Baghdad, Iraq. The study was conducted according to the guidelines from the Declaration of Helsinki with approval from a local ethical review board. All patients gave written informed consent. The criteria of inclusion are obese patients with T2D using oral hypoglycemic agents. Obesity means a BMI of ≥ 30 kg/m^2. All the patients were on the glibenclamide (up to 12.5 mg daily) and metformin (up to 1,750 mg daily). The present study excluded the patients with a history of rheumatoid arthritis, hematological, neoplastic, renal, hepatic or thyroid diseases, or patients receiving treatment with anti-inflammatory drugs. Patients with acute or chronic infections and autoimmune disease (e.g. systemic lupus erythematous) were also excluded from the study. Demographic data, medical history and treatment were obtained from the case-sheet data in the center. Modifiable risk factors, events or complications, and current therapy were recorded. A person who reported smoking on admission was defined as current smoker. The following anthropometric measurements are determined: height (m), weight (kg), waist circumference (cm). The BMI and waist/height ratios were calculated taking the cut-off level of BMI ≥ 30 kg/m^2 and waist to hip ratio ≥ 0.5 as an indication of obesity. The blood pressure (mm Hg) was measured on sitting position and the mean of three readings was taken. The difference between systolic and diastolic

Table 2. Cardio-Metabolic Risk Factors

Variables	Women (n = 100)	Men (n = 50)	P value
Fasting serum glucose (mg/dL)	210.2 ± 35.7	211.6 ± 33.2	0.806
Glycosylated hemoglobin ($HbA1_c$ %)	8.1 ± 0.6	8.1 ± 0.7	0.755
Arterial blood pressure (mm Hg)			
Systolic	135.2 ± 8.5	135.9 ± 8.7	0.653
Diastolic	85.2 ± 4.7	86 ± 4.6	0.303
Mean	101.8 ± 4.8	102.6 ± 5.1	0.368
Pulse pressure	50.0 ± 8.4	49.9 ± 7.8	0.908
Fasting serum lipid profile			
Triglycerides (mg/dL)	195.3 ± 83.0	184.1 ± 76.0	0.408
Total cholesterol (mg/dL)	211.1 ± 68.2	203.5 ± 60.5	0.487
High density lipoprotein (mg/dL)	51.6 ± 11.2	54.1 ± 11.0	0.195
Atherogenic lipoprotein (mg/dL)	150.1 ± 67.6	128.9 ± 60.6	0.309
Atherogenic index	0.553 ± 0.271	0.509 ± 0.254	0.338
High sensitivity C-reactive protein (mg/L)	5.0 ± 0.66	4.9 ± 0.65	0.580

The results are expressed as number and mean ± SD.

Table 3. Serum Thyroid Hormones

Variables	Women (n = 100)	Men (n = 50)	P value
Thyroid stimulating hormone (TSH)			
< 0.3 mIU/L	18 (18)	13 (26)	0.253
> 0.6 mIU/L	68 (68)	30 (60)	0.331
Mean ± SD (median)	6.2 ± 5.2 (7.1)	4.83 ± 4.24 (5.57)	0.096
Thyroxin (T4)			
< 60 nmol/L	22 (22)	8 (16)	0.386
> 140 nmol/L	11 (11)	8 (16)	0.385
Mean ± SD (median)	96.5 ± 35.1 (98.5)	105.5 ± 33.8 (122)	0.133
Triiodothyronine (T3)			
< 0.9 nmol/L	19 (19)	4 (8)	0.163
> 2.5 nmol/L	42 (42)	30 (60)	0.037*
Mean ± SD (median)	2.14 ± 1.2 (2.2)	2.34 ± 1.07 (2.7)	0.301

*Significant. The results are expressed as number (%) and mean ± SD (median).

blood pressure represented the pulse pressure and the mean arterial blood pressure was equal to diastolic blood pressure + 1/3 pulse pressure.

Peripheral venous blood was drawn immediately after admission into tubes, then the samples were centrifuged at 2,500 rpm for 10 min, and the sera were separated for determination of fasting serum glucose, $HbA1_c$ (%) fasting lipid profile and thyroid hormones: TSH, total thyroxin (T4) and total triiodothyronine (T3).

The determinants of lipid profile included fasting serum TC, TG, and HDL-c. The non-HDL-c lipoprotein (LDL-c) is determined by using the equation that was described by Rungtanapirom et al) [12]

Determined LDL = 0.98 (TC - HDL) - 0.12 TG + 0.1 Age + 2.4 Sex + 0.2 BMI (for male = 1 and for female = 2)

The atherogenic index was calculated by estimating the log of the ratio TG to HDL values. Quantitative determination of serum high sensitive C-reactive protein (hsCRP) was determined using the enzyme-linked immunosorbent assay (ELISA) technique. The following values indicated the level of cardiovascular event risk: < 1.0 mg/L (low risk), 1.0 - 3.0 mg/L (intermediate risk) and > 3.0 mg/L (high risk). The determination of thyroid hormones was carried on using MiniVidas equipment and the kits purchased from bioMerieux, France. The normal ranges of thyroid hormones are TSH: 0.3 - 0.6 mIU/L, T4: 60 - 140 nmol/L, and T3: 0.9 - 2.5 nmol/L.

Statistical analysis

Data are expressed as number, percent, mean ± SD or median. Unpaired Student's *t*-test was used to evaluate differences between the two groups and the simple correlation test was applied for the association between the independent and dependent factors. For all tests, a two-tailed $P \leq 0.05$ was considered statistically significant. All calculations were made using Excel 2003 program for Windows.

Results

Table 1 shows the characteristics of patient. There was non-significant difference between men and women regarding the age and the duration of diabetes. Family history was reported in 24% in women compared with 32% in men which did not reach significant level. The results of anthropometric measurements showed significant high body weight and BMI in women compared with men while the waist circumference and waist to height ratio did not show significant differences.

Table 2 shows the profile of cardio-metabolic risk factors. The glycemic status that was determined by fasting serum glucose and glycosylated hemoglobin indicated that the patients of both genders were uncontrolled diabetes. There was non-significant difference between men and women with respect to the glycemic status. There was non-significant difference between the blood pressures (systolic, diastolic, mean and pulse) between women and men. The mean values of systolic and diastolic blood pressure exceeded the upper limits of 130 mm Hg systolic and 85 mm Hg diastolic (cut-off values in diabetes). Fasting serum profile indicated that both genders are at risk of cardiovascular events. The mean values of fasting serum TG, atherogenic lipoprotein and atherogenic index exceed the upper normal values. The mean value of HDL-c achieved the level within the normal range. There were non-significant differences between women and men in the mean values of lipid profile. The mean value of hsCRP which amounted more than 3 mg/L indicated that all patients were at high risk of cardiovascular events. Table 3 shows changes in the thyroid function reflected by fluctuation in the thyroid hormone levels. The mean level of TSH was non-significantly higher in women compared with men. Normal range TSH hormone level was reported in 16 out of 100 (16%) women compared with seven out of 50 (14%) men, a difference that did not reach significant level. The low level of TSH was found in higher percent men compared with women (26% versus 18%). The mean levels of T4 and T3

Table 4. Correlation Coefficient of the Relationship Between Thyroid Hormones and Cardio-Metabolic Risk Factors

Variables	Women (n = 100)	P value	Men (n = 50)	P value
Thyroid stimulating hormone (TSH) versus				
Body mass index	0.429	0.000*	0.536	0.000*
Waist circumference	0.484	0.000*	0.716	0.000*
Mean arterial blood pressure	0.219	0.028*	0.445	0.001*
Fasting serum glucose	0.071	0.482	0.244	0.087
Glycosylated hemoglobin ($HBA1_c$ %)	0.273	0.006*	0.318	0.024*
Fasting serum triglycerides	0.545	0.000*	0.761	0.000*
Fasting serum high density lipoprotein	-0.469	0.000*	-0.809	0.000*
High sensitivity C-reactive protein	0.025	0.804	0.143	0.321
Thyroxine (T4) versus				
Body mass index	-0.576	0.000*	-0.812	0.000*
Waist circumference	-0.811	0.000*	-0.819	0.000*
Mean arterial blood pressure	-0.496	0.000*	-0.534	0.000*
Fasting serum glucose	-0.101	0.317	-0.371	0.007*
Glycosylated hemoglobin ($HBA1_c$ %)	-0.334	0.000*	-0.099	0.493
Fasting serum triglycerides	-0.843	0.000*	-0.850	0.000*
Fasting serum high density lipoprotein	0.790	0.000*	0.821	0.000*
High sensitivity C-reactive protein	-0.282	0.004*	-0.473	0.000*
Triiodothyronine (T3) versus				
Body mass index	-0.475	0.000*	-0.710	0.000*
Waist circumference	-0.668	0.000*	-0.775	0.000*
Mean arterial blood pressure	-0.351	0.000*	-0.430	0.001*
Fasting serum glucose	-0.190	0.058	-0.436	0.001*
Glycosylated hemoglobin ($HBA1_c$ %)	-0.318	0.001*	-0.314	0.026*
Fasting serum triglycerides	-0.760	0.000*	-0.826	0.000*
Fasting serum high density lipoprotein	0.704	0.000*	0.820	0.000*
High sensitivity C-reactive protein	-0.301	0.002*	-0.378	0.007*

*Significant. The results are expressed as correlation coefficient (r).

were non-significantly higher in men compared with women. Table 4 shows the correlations between the cardio-metabolic risk factors and the thyroid hormones. TSH was significantly correlated (positively) with BMI, waist circumference, mean arterial blood pressure, and glycosylated hemoglobin, while it correlated inversely with HDL-c. Non-significant correlations were observed with fasting serum glucose and hsCRP. The power of correlation as assessed by correlation coefficient (r) was higher in men compared with women. The opposite pictures were observed with T4 or T3. Both hormones were significantly correlated in an inverse pattern with cardio-metabolic risk factors and positively correlated with HDL-c. Again the higher coefficient factors of these associations were found in men compared with women.

Discussion

The results of this study show fluctuation in the serum TSH, T3 and T4 indicating thyroid gland dysfunction in uncontrolled T2D. Moreover, the higher serum T3 or T4 associated with lower cardio-metabolic risk factors. These changes are well observed in men compared with women indicating the alteration in thyroid gland function in T2D is gender-based effect. Obesity as a cause of insulin resistance may play a role in thyroid dysfunction. There is evidence that low free T4 is associated with insulin resistance [13]. Therefore, it is possible to attribute the findings of this study to the obesity as the BMI value is significantly less in men compared with women. Solanki et al reported significant correlation between BMI and TSH in healthy adults but the authors did not highlight the difference between men and women [14]. As shown in Table 2, there were no significant differences between men and women regarding the cardio-metabolic risk factors which indicated that the results of this study was not biased with variations in the clinical presentation. Low serum T3 and T4, and low TSH levels are presented in high percent in women compared with men and such subclinical hypothyroidism status is presented

with cardio-metabolic risk factors as shown in Table 2. This finding confirmed the results reported by Pesic et al but again the authors did not demonstrate the effect of gender [15]. The positive correlation between glycosylated hemoglobin and TSH, and an inverse correlation with T3 or T4 in T2D patients confirmed a previous study carried on non-diabetic subject [16]. This observation may be attributed to the catabolic effect of thyroid hormones as well as the insulin resistant status on the albumin metabolism which reflected on the glycosylated hemoglobin [17]. In this study the hsCRP as an inflammatory biomarker does not significantly correlate with TSH, but an inverse significant correlation with T3 or T4 was observed with a higher coefficient correlation in male. This observation agreed with the previous results that reported an association of higher circulating levels of inflammatory markers with lower levels of free serum T3 in elderly population [18]. A prominent gender-based effect of thyroid hormones and TSH in relation to the HDL-c was observed in this study. Triolo et al observed that plasma glucose interacted positively with free T4 on HDL antioxidative capacity, and that in chronic hyperglycemia, the low free T4 within the euthyroid range involved in the diminished HDL antioxidative capacity [19]. One of the limitations of this study is non-diabetic healthy subjects are not included and thereby the gender-based effect is limited in the T2D. It concludes that there are alterations in the thyroid gland function in obese T2D patients and the levels of thyroid hormones (T3 and T4) were significantly and inversely correlated with cardio-metabolic risk factors which prominently were observed in men.

Conflict of Interest

Nil.

References

1. Friedrich N, Rosskopf D, Brabant G, Volzke H, Nauck M, Wallaschofski H. Associations of anthropometric parameters with serum TSH, prolactin, IGF-I, and testosterone levels: results of the study of health in Pomerania (SHIP). Exp Clin Endocrinol Diabetes. 2010;118(4):266-273.
2. Oh JY, Sung YA, Lee HJ. Elevated thyroid stimulating hormone levels are associated with metabolic syndrome in euthyroid young women. Korean J Intern Med. 2013;28(2):180-186.
3. Aypak C, Turedi O, Yuce A, Gorpelioglu S. Thyroid-stimulating hormone (TSH) level in nutritionally obese children and metabolic co-morbidity. J Pediatr Endocrinol Metab. 2013;26(7-8):703-708.
4. Radhakishun NN, van Vliet M, von Rosenstiel IA, Weijer O, Beijnen JH, Brandjes DP, Diamant M. Increasing thyroid-stimulating hormone is associated with impaired glucose metabolism in euthyroid obese children and adolescents. J Pediatr Endocrinol Metab. 2013;26(5-6):531-537.
5. Topsakal S, Yerlikaya E, Akin F, Kaptanoglu B, Erurker T. Relation with HOMA-IR and thyroid hormones in obese Turkish women with metabolic syndrome. Eat Weight Disord. 2012;17(1):e57-61.
6. Garduno-Garcia Jde J, Alvirde-Garcia U, Lopez-Carrasco G, Padilla Mendoza ME, Mehta R, Arellano-Campos O, Choza R, et al. TSH and free thyroxine concentrations are associated with differing metabolic markers in euthyroid subjects. Eur J Endocrinol. 2010;163(2):273-278.
7. Diez JJ, Iglesias P. Serum cholesterol and triglyceride concentrations in diabetic patients with subclinical hypothyroidism. Endocrinol Nutr. 2014;61(8):419-425.
8. Lupoli R, Di Minno A, Tortora A, Ambrosino P, Lupoli GA, Di Minno MN. Effects of treatment with metformin on TSH levels: a meta-analysis of literature studies. J Clin Endocrinol Metab. 2014;99(1):E143-148.
9. Wang YM, Ling Y, Gao X. [Effects of thyroid hormone on islet beta cell function among type 2 diabetics with normal thyroid function]. Zhonghua Yi Xue Za Zhi. 2013;93(14):1084-1088.
10. Kouidhi S, Berhouma R, Ammar M, Rouissi K, Jarboui S, Clerget-Froidevaux MS, Seugnet I, et al. Relationship of thyroid function with obesity and type 2 diabetes in euthyroid Tunisian subjects. Endocr Res. 2013;38(1):15-23.
11. Tarcin O, Abanonu GB, Yazici D. Association of metabolic syndrome parameters with TT3 and FT3/FT4 ratio in obese Turkish population. Metab Syndr Relat Disord. 2012;10(2):137-142.
12. Rungtanapirom S, Ongphiphadhanakul B, Kiatbamrungpunt T, Bhakdikul J, Archavanuntakun S, Taerakul C, Pongsanguansin J, et al. Comparative study of direct-measured and calculated LDL in clinical use. J Med Assoc Thai. 2008;91(7):989-994.
13. Deetman PE, Bakker SJ, Kwakernaak AJ, Navis G, Dullaart RP. The relationship of the anti-oxidant bilirubin with free thyroxine is modified by insulin resistance in euthyroid subjects. PLoS One. 2014;9(3):e90886.
14. Solanki A, Bansal S, Jindal S, Saxena V, Shukla US. Relationship of serum thyroid stimulating hormone with body mass index in healthy adults. Indian J Endocrinol Metab. 2013;17(Suppl 1):S167-169.
15. Pesic M, Antic S, Kocic R, Radojkovic D, Radenkovic S. [Cardiovascular risk factors in patients with subclinical hypothyroidism]. Vojnosanit Pregl. 2007;64(11):749-752.
16. Koga M, Murai J, Saito H, Matsumoto S, Kasayama S. Effects of thyroid hormone on serum glycated albumin levels: study on non-diabetic subjects. Diabetes Res Clin Pract. 2009;84(2):163-167.
17. Bae JC, Seo SH, Hur KY, Kim JH, Lee MS, Lee MK, Lee WY, et al. Association between Serum Albumin, Insulin Resistance, and Incident Diabetes in Nondiabetic Subjects. Endocrinol Metab (Seoul). 2013;28(1):26-32.
18. Rozing MP, Westendorp RG, Maier AB, Wijsman CA, Frolich M, de Craen AJ, van Heemst D. Serum triiodothyronine levels and inflammatory cytokine production capacity. Age (Dordr). 2012;34(1):195-201.
19. Triolo M, de Boer JF, Annema W, Kwakernaak AJ, Tietge UJ, Dullaart RP. Low normal free T4 confers decreased high-density lipoprotein antioxidative functionality in the context of hyperglycaemia. Clin Endocrinol (Oxf). 2013;79(3):416-423.