International Journal of Bioassays
ISSN: 2278-778X
CODEN: IJBNHY
OPEN ACCESS

Original Research Article

ASSOCIATION OF THYROID-STIMULATING HORMONE AND THYROID HORMONES WITH LIPID PROFILE IN GHANAIAN EUTHYROID PATIENTS WITH TYPE 2 DIABETES

Nii Ayite Aryee[1]* and Emmanuel Ayitey Tagoe[2]

[1]Department of Medical Biochemistry, School of Biomedical and Allied Health Sciences, College of Health Sciences, University of Ghana, Legon

[2]Department of Medical Laboratory Sciences, School of Biomedical and Allied Health Sciences, College of Health Sciences, University of Ghana, Legon

Received for publication: August 29, 2014; **Accepted:** September 18, 2014

Abstract: Increasing evidence suggests that thyroid stimulating hormone (TSH) may exert extra-thyroidal effects and modulate the profile of blood lipids. The aim of this study was to determine the association between TSH levels, thyroid hormones, thyroxine (FT4), free triiodothyronine (FT3) and lipid profile in euthyroid type 2 diabetic and non-diabetic subjects with elevated cholesterol levels. Serum levels of TSH, FT4 and FT3 in diabetic and non-diabetic euthyroid subjects with normal and elevated cholesterol levels were assayed. Total cholesterol (TC), triglyceride (TG) and high-density lipoprotein (HDL-c) cholesterol were also analyzed. Serum TSH levels were found to be lower in individuals with elevated cholesterol. Serum TSH levels correlated positively with TC, LDL-c and HDL-c but showed a negative relationship with TG and FPG in diabetics with elevated cholesterol. FT3 showed negative correlation with lipid parameters and FPG except HDL-c. However, serum FT4 levels were not significantly different between study groups. We infer that TSH may be one of many biochemical modulators of circulatory lipids. Our results suggest that reduction in TSH levels may play a role in the elevation of lipids irrespective of diabetic status. An assessment of TSH status may have wide-ranging clinical significance in the management of hypercholesterolemia in both diabetic and non-diabetic individuals.

Key Words: Thyroid Stimulating Hormone, TSH, Management

INTRODUCTION

Thyroid hormones have important roles in regulating hepatic lipid, cholesterol, and glucose metabolism [1]. Hypothyroidism, like dyslipidemia, is a patho-physiological condition frequently associated with disorders of lipid metabolism, and a major risk factor for coronary disease [2]. The consequences of thyroid dysfunction may be various quantitative and/or qualitative changes of triglycerides, phospholipids, cholesterol, and other lipoproteins [3]. Dyslipidemia, resulting from thyroid dysfunction, increases risk for cardiovascular disease [4, 5, 6]. The occurrence of insulin resistance has been noted in hypothyroidism [7, 8]. Although there have been several large cross-sectional studies examining the association between thyroid dysfunction and lipid metabolic abnormalities, few have studied euthyroid subjects with type 2 diabetes. Previous studies have shown that thyroid stimulating hormone (TSH), free thyroxine (FT4) and free triiodothyronine (FT3) are significantly associated with lipid profile in the euthyroid population, regardless of gender [8, 9]. The influence of TSH on lipid profile has been assumed to be mediated indirectly, through its effect on thyroid hormones. However, additional evidence suggests that this association is partially contributed by the direct extra-thyroidal effect of TSH on lipid profile [10, 11]. It has previously been observed that almost 10% of asymptomatic hyper cholesterolemic patients have subclinical hypothyroidism [12]. In that study, it was observed that even TSH levels in the upper normal range may be associated with lipid abnormalities [12]. Our recent study reported a reduced level of TSH and FT3 in type 2 diabetic patients with elevated total cholesterol, triglycerides and increased cardiovascular risk [13]. This observation raises the interesting possibility that even the phase preceding the so called 'subclinical' hypothyroidism may be associated with lipid abnormalities, and that this phase may not be as 'normal' as previously thought. Detection of "atypical" thyroid hormone levels in the early stage of diabetes will contribute to the management of diabetic patients and reduce co-morbidities associated with thyroid dysfunction and dyslipidemia in diabetes. Recent studies have pointed to the fact that there could be some relationship between thyroid hormones and components of lipid parameters such as cholesterol, even in euthyroid individuals with insulin resistance [14]. The aim of this study was therefore to elucidate the association between lipid profile and thyroid hormone parameters in the setting of borderline cholesterol elevation.

MATERIALS AND METHODS

Subjects

Patients for this study were recruited from the out-patients' clinic of the National Diabetes Management and Research Centre (NDMRC) of the Korle-Bu Teaching Hospital, Accra. Type 2 diabetes

***Corresponding Author:**
Dr. Nii Ayite Aryee,
Department of Medical Biochemistry,
School of Biomedical and Allied Health Sciences,
College of Health Sciences,
University of Ghana, Legon.

mellitus (T2DM) was diagnosed according to the guidelines of the World Health Organization Consultation Report on the definition of diabetes [15]. 79 Ghanaian T2DM patients, and an age-matched control group of 51 non-diabetic, apparently healthy individuals with normal fasting blood glucose, and a negative family history of diabetes among first degree relatives constituted the study group. Informed consent was obtained from all subjects. Subjects were further divided into four groups based upon serum total cholesterol (TC) levels. T2DM subjects with total cholesterol of 5.5 mmol/l or higher (Group 1), T2DM subjects with total cholesterol lower than 5.5 mmol/l (Group 2), apparently healthy controls with total cholesterol of 5.5 mmol/l or higher (Control 1), and Control 2, constituted apparently healthy controls subjects with total cholesterol lower than 5.5 mmol/l. This study was approved by the Ethical and Protocol Review Committee of the School of Allied Health Sciences of the College of Health Sciences, University of Ghana, Legon.

Clinical and biochemical measurements

Demographic data including age, sex, duration of diabetes, weight, height and waist-hip ratio were collected using standard questionnaires at recruitment. Blood pressure (BP) was measured by first allowing participants to rest for 15 minutes prior to measurement. Venous blood samples were drawn after an overnight fast and distributed into fluoride and serum collection tubes respectively. Plasma obtained from fluoride tubes after centrifugation at 4000 rpm for 10 min was used for fasting plasma glucose (FPG) analysis. Total cholesterol (TC), triglycerides (TG), and HDL-cholesterol (HDL-c) were measured by automated enzymatic methods (Vital Scientific Microlab 300M, VSM 300). LDL-cholesterol (LDL-c) was calculated according to Friedewald formula [16]. Thyroid hormone profile (TSH, FT3 and FT4) for all subjects were assayed using enzyme-linked immunosorbent assay (ELISA), (Human, Germany) and Labsystems Multiscan-352 plate reader (Finland).

Statistical Analysis

Baseline characteristics, clinical and biochemical measurements were expressed as Mean ± SD (standard deviation) for continuous variables, and as percentages for categorical variables. ANOVA (Graphpad 3.0) was used to compare the mean difference of the groups. Pearson correlation coefficient (r) was used for interdependency of parameters. $P \leq 0.05$ was considered statistically significant for all analyses.

RESULTS

Baseline characteristics and clinical/ biochemical parameters of the study groups are shown in Table 1. There were significantly more female subjects in the type 2 diabetes Mellitus (T2DM) group than in the non-diabetic control group. T2DM patients were not significantly different from the control group with respect to age, BMI and waist-hip ratio ($P > 0.05$). T2DM patients however had elevated systolic and diastolic blood pressure with no statistically significant mean difference when compared to the controls ($P>0.05$). T2DM subjects also had significantly higher plasma glucose levels than controls. The average duration for subjects who had been diagnosed with T2DM was 9 years. These individuals had a mean fasting plasma blood glucose concentration of 9.0mmol/l, which was significantly higher than in controls. Cardiovascular risk was significantly higher in diabetic individuals with elevated cholesterol when compared to their non-diabetics counterparts, and individuals with apparently normal cholesterol levels. Cardiovascular risk was independent of diabetic status. The lipid profiles of all study groups are presented in Table 2. Mean serum levels of HDL-c did not show any significant difference between T2DM and non-diabetic individuals. Multiple comparison test of HDL-c levels after one way ANOVA described an insignificant difference between all study groups. T2DM patients had higher TC and TG than non-diabetics. LDL-c was significantly elevated in group 1 compared to controls, but was lower in group 2 when compared to controls. Thyroid hormone profile (TSH, FT3 and FT4) for the study groups are shown in Table 3. Serum TSH levels were not significantly different between all study groups except for between groups 2 and control 2 ($P < 0.05$). FT3 mean difference between study group 1 and control 2, group 2 and control 1, and between controls were significant ($P < 0.05$). However, serum FT4 levels were not significantly different between study groups. Serum TSH levels correlated positively with TC, LDL-c and HDL-c, but showed a negative relationship with TG and FPG in diabetics with elevated cholesterol (group 1). Serum FT3 levels of individuals in study group 1 was weakly associated with serum lipids and FPG.

Table 1: Baseline characteristics and clinical variables of the study groups

Variable	Group 1 (N= 35)	Group 2 (N = 44)	Control 1 (N= 11)	Control 2 (N = 40)	*P*-value (ANOVA)
Gender: M n (%)	13(37.1)	12(27.3)	5 (45.5)	21 (52.5)	
F n (%)	22(62.9)	32(72.7)	6 (54.5)	19 (47.5)	
Age (years)	53.83 ± 10.35	52.32 ± 10.53	49.09 ± 7.12	51.30 ± 13.45	0.6058
SBP (mmHg)	133.19 ± 20.99	124.25 ± 17.61	122.32 ± 18.69	122.03 ± 23.66	0.0999
DBP (mmHg)	74.93 ± 11.19	74.26 ± 10.50	73.05 ± 13.60	70.99 ± 16.81	0.5579
BMI (kg/m^2)	28.09 ± 6.85	28.63 ± 6.00	28.00 ± 5.18	27.31 ± 8.92	0.8707
WHR	1.14 ± 0.28	1.08 ± 0.12	1.09 ± 0.08	1.15 ± 0.28	0.4678
FPG (mmol/l)	9.87 ± 4.95** †††	9.45 ± 4.42 †† ***	5.54 ± 0.65	5.01 ± 0.61	< 0.0001
DD (years)	9.86 ± 6.88	9.56 ± 7.24	-	-	-
2-Hr OGTT	-	-	6.63 ± 1.02	5.89 ± 1.12	-

Group 1 = D2M subjects with cholesterol level > 5.5 mmol/l; Group 2 = D2M subjects with cholesterol level < 5.5 mmol/l; Control 1 = Control subjects with cholesterol level > 5.5 mmol/l; Control 2 = Control subjects with cholesterol level < 5.5 mmol/l; F = Females; M = Males; SBP = Systolic blood pressure; DBP = Diastolic blood pressure; BMI – Body mass index;
WHR = Waist-to-hip ratio; DD = Duration of diabetes.
*significant with Control 1 (*P* < 0.05); ** significant with Control 2 (*P* < 0.01); ***significant with Control 2 (*P* < 0.001);
† significant with control 2 (*P* < 0.05); †† significant with Control 2 (*P* < 0.01), †††significant with Control 2 (*P* < 0.001). 2-HR OGTT = 2-hour oral glucose tolerance test.

Table 2: Lipid profile of the study groups

Variable	Group 1 (N= 35)	Group 2 (N = 44)	Control 1 (N= 11)	Control 2 (N = 40)	*P*-value (ANOVA)
TC (mmol/l)	6.93 ± 1.69 †††	4.12 ± 0.75***	6.11 ± 0.85	4.18 ±0.67	< 0.0001
TG (mmol/l)	1.58 ± 0.61 †††	1.23 ± 0.34 †	1.21 ± 0.50	0.93 ± 0.47	<0.0001
HDL-c (mmol/l)	1.25 ± 0.41	1.26 ± 0.28	1.32 ± 0.14	1.22 ± 0.25	0.7979
LDL-c (mmol/l)	4.96 ± 1.69 †††	2.29 ±0.84***	4.24 ± 0.90	2.50 ± 0.63	<0.0001
CVD risk	6.18 ± 2.73 †††	3.46 ± 1.10	4.70 ± 0.92	3.54 ± 0.75	<0.0001

TC = Total cholesterol; TG = triglyceride; HDL-c = high density lipoprotein; LDL-c = low density lipoprotein; CVD = cardiovascular disease.
*significant with Control 1 (*P* < 0.05); ** significant with Control 1 (*P* < 0.01), ***significant with Control 1 (*P* < 0.001); †significant with Control 2 (*P* < 0.05); ††significant with Control 2 (p < 0.01), ††† significant with Control 2 (*P* < 0.001).

Table 3: Thyroid hormone profile (TSH, FT3 and FT4) for the study groups

Variable	Group 1 (N= 35)	Group 2 (N = 44)	Control 1 (N= 11)	Control 2 (N = 40)	p-value (ANOVA)
TSH (mUI/ml)	1.59 ± 1.24 *	1.91 ± 1.07	1.83 ± 0.87	2.36 ± 1.12	0.0310
FT3 (pg/dl)	1.40 ± 0.85 †††	1.00 ± 0.91 *†††	1.74 ± 0.48	2.26 ± 0.42	<0.0001
FT4 (ng/dl)	1.06 ± 0.33	1.04 ± 0.25	1.16 ± 0.17	1.05 ± 0.28	0.6380

TSH = thyroid stimulating hormone; FT3 = free triiodothyroxine; FT4 = thyronine.
*significant with Control 1 (*P* < 0.05); **significant with Control 1 (*P* < 0.01); ***significant with Control 1 (*P* < 0.001); †significant with Control 2 (*P* < 0.05); † †significant with Control 2 (*P* < 0.01); † † significant with Control 2 (*P* < 0.001).

Table 4: Correlation of serum FT3, TSH with Total Cholesterol, Triglyceride, HDL-c, LDL-c and Fasting blood glucose in the study subjects (Group 1 subjects).

Parameter	TSH		FT3	
	r	p	r	p
TC	0.249	0.0784	-0.087	0.5455
TG	-0.171	0.2315	-0.021	0.8834
HDL-c	0.140	0.3272	0.033	0.8179
LDL-c	0.238	0.0921	-0.082	0.5696
FPS	-0.124	0.3869	-0.234	0.0983

TC = Total cholesterol; TG = triglyceride; HDL-c = high density lipoprotein; LDL-c = low density lipoprotein. p value less than 0.05 is considered significant.

DISCUSSION

In this study, BMI, SBP and DBP of type 2 diabetes mellitus (T2DM) patients compared with the non-diabetics showed no significant difference. In addition to elevated FPG, TC and TG levels were also found to be higher in these patients than in non-diabetic subjects. Elevated LDL-c was associated with higher cardiovascular risk. These results conform to the pattern of many studies that indicate that T2DM individuals are more likely to have higher levels of FPG and circulatory lipids than non-diabetics [17, 18, 19, 20]. However, TSH levels were lower in group 1 compared to the rest of the study groups. Low TSH levels with concomitant elevation of most serum lipids (TC, TG and LDL-c) as seen in study groups 1 and control 1 emphasizes the hormonal influence in maintaining a balance in circulatory lipids. This observation suggests that a reduction in the level of TSH may play a role in the elevation of lipids irrespective of diabetic status. In patients with elevated cholesterol (group 1), TSH levels showed a more positive correlation with most lipid parameters than FT3. Our previous study showed significantly reduced TSH levels with elevated lipids in diabetic patients than in non-diabetics [13]. In one recent study, 10.7% of euthyroid subjects with low TSH were found to be hypercholesterolemic [10]. Another study has shown that the TSH level was an independent factor predictive of increased lipid abnormality in euthyroid non-smokers with asymptomatic cardiac

heart disease [21]. However, no change in TC levels, elevated TG and HDL-c in diabetics with reduced levels of TSH compared with non-diabetics has been reported [22]. Several factors including modification of the synthesis and release of thyroid releasing hormone (TRH), the production of thyroid hormone binding inhibitor (THBI) and glycemic status have been implicated in reduced TSH levels in diabetic patients [23, 24]. In apparently healthy individuals, thyroid dysfunction is mostly attributed to iodine deficiency and age [25, 26]. TSH regulates serum thyroid hormone levels, which in turn affects lipid synthesis, uptake, release, and degradation. We infer from this study that an assessment of thyroid function/status in both diabetic and non-diabetic individuals within the setting of borderline cholesterol elevation or hyper-cholesterolemia could be an intervention that would have considerable clinical significance.

CONCLUSION

TSH may be one of many biochemical modulators of circulatory lipids. The study suggests that reduction in TSH levels may play a role in the elevation of lipids irrespective of diabetic status. An assessment of TSH levels could have wide-ranging clinical significance in the management of hypercholesterolemia in both diabetic and non-diabetic individuals.

REFERENCES

1. Mullur R, Yan-Yun L, Brent GA, Thyroid hormone regulation of metabolism, Physiological Reviews, 2014, 94, 355-382.
2. Limbu YR, Rai SK, Ono K, Lipid profile of adult Nepalese population, Nepal Medical College Journal, 2008, 1, 4-7.
3. Zhu X, Cheng SY, New insights into regulation of lipid metabolism by thyroid hormone, Current Opinion in Endocrinology, Diabetes and Obesity, 2010, 17(5), 408–413.
4. Klein I, Ojamaa K, Thyroid hormone and the cardiovascular system, New Engl J Med 2001, 344(7), 501–509.
5. Biondi B, Klein I, Hypothyroidism as a risk factor for cardiovascular disease, Endocrine, 2004, 24(1), 1–13.
6. Biondi B, Kahaly GJ, Cardiovascular involvement in patients with different causes of hyperthyroidism, Nature Reviews Endocrinology, 2010, 6(8), 431–443.
7. Chubb SA, Davis WA, Davis TM, Interactions among thyroid function, insulin sensitivity, and serum lipid concentrations. The Fremantle diabetes study, J Clin Endocrinol Metab, 2005, 90 (9), 5317-5320.
8. Roos A, Bakker SJL, Links TP, Gans ROB, Wolffenbuttel BHR, Thyroid function is associated with components of the Metabolic Syndrome in Euthyroid Subjects, J Clin Endocrinol Metab, 2007, 92, 491-496.
9. Garduno-Garcia JJ, Alvirde-Garcia U, Lopez-Carrasco G, Padilla-Mendoza ME, *et al.*, TSH and free thyroxine concentrations are associated with differing metabolic markers in euthyroid subjects, Eur J Endocrinol, 2010, 163, 273–278.
10. Wang F, Tan Y, Wang C, Zhang X, Zhao Y, Song X, *et al.*, Thyroid-stimulating hormone levels within the reference range are associated with serum lipid profiles independent of thyroid hormones, J Clin Endocrinol Metab, 2012, 97, 2724-2731.
11. Ruhla S, Weickert MO, Arafat AM, Osterhoff M, Isken F, Spranger J, *et al.*, A high normal TSH is associated with the metabolic syndrome, Clin Endocrinol, 2010, 72, 696-701.
12. Pallas D, Koutras DA, Adamopoulos P, Marafelia P, Souvatzoglou A, Piperingos G, *et al.*, Increased mean serum TSH in apparently euthyroid hyper cholesterolemic patients. Does it mean occult hypothyroidism?, J Endocrinol Invest, 1991, 14, 743–746.
13. Tagoe EA, Azasu H, Annan DA, Ababio GK, Asare-Anane H, Aryee NA, Evaluation of thyroid profile in Ghanaian patients with Type 2 diabetes, Int J Adv Res, 2014, 2(4), 602-609.
14. Kim BJ, Kim TY, Koh JM, Kim HK, Park JY, Lee K, *et al.*, Relationship between serum free T4 (FT4) levels and metabolic syndrome (MS) and its components in healthy euthyroid subjects, Clin Endocrinol, 2009, 70, 152-160.
15. World Health Organization, WHO consultation report, Definition, diagnosis and classification of diabetes and its complications, 1999, WHO Geneva.
16. Friedewald WT, Levy RI, Fredrickson DS, Estimation of the concentration of low density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge, Clin Chem, 1972, 18, 499–502.
17. Sawant AM, Shetty D, Mankeshwar R, Ashavaid TF, Prevalence of dyslipidemia in a young adult Indian population, JAPI, 2008, 56, 99-102.
18. Toruner F, Altinova AE, Karakoc A, Risk factors for cardiovascular disease in patients with subclinical hypothyroidism, Adv Ther, 2008, 25, 430-437.
19. Gordon L, Ragoobirsingh D, St Errol YA, Morrison EYA, Choo-Kang E, McGrowder D, *et al.*, Lipid profile of type 2 diabetic and hypertensive patients in the Jamaican population, J Lab Physicians, 2010, 2(1), 25–30.
20. Singh G, Gupta V, Sharma AK, Gupta N, Evaluation of Thyroid Dysfunction among type 2 diabetic Punjabi Population, Adv. Biores, 2011, 2(2), 3-9.

21. Wanjia X, Chenggang W, Aihong W, Xiaomei Y, Jiajun Z, Chunxiao Y, *et al.,* A high normal TSH level is associated with an atherogenic lipid profile in euthyroid non-smokers with newly diagnosed asymptomatic coronary heart disease, Lipids Health Dis, 2012, 11, 44.

22. Pasupathi P, Bakthavathsalam G, Ganesan-Saravanan G, Sundaramoorthi S, Screening for thyroid dysfunction in the diabetic/non-diabetic population, Thyroid Science, 2008, 3(8), 1-6.

23. de Greef WJ, Rondeel JM, Heide R, Klootwijk W, Visser TJ, Is thyrotropin-releasing hormone immunoreactivity in peripheral blood an estimate for hypothalamic thyrotropin-releasing hormone release?, Acta Endocrinol (Copenh), 1992, 126(3), 276-81.

24. Suzuki J, Nanno M, Gemma R, Tanaka I, Taminato T, Yoshimi T, The mechanism of thyroid hormone abnormalities in patients with Diabetes mellitus, Nippon Niabunpi Gakki Zasshi, 1994, 7, 465-470.

25. González-Rodríguez LA, Felici-Giovanini ME, Haddock L, Thyroid Dysfunction in an Adult Female Population: A population-based study of Latin American Vertebral Osteoporosis Study (LAVOS)-Puerto Rico Site, P R Health Sci J, 2013, 32(2), 57–62.

26. Menon VU, Sundaram KR, Unnikrishnan AG, Jayakumar RV, Nair V, Kumar H, High prevalence of undetected thyroid disorders in an iodine sufficient adult South Indian population, J Indian Med Assoc, 2009, 107(2), 72-77.

Source of support: Nil
Conflict of interest: None Declared