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Type 2 Diabetes Mellitus and Subclinical Hypothyroidism Coincidence and Its Effect on Triglyceride Glucose Index (TyG) and Atherogenic Index of Plasma (AIP)

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ABSTRACT

Objective: *Type 2 Diabetes Mellitus and subclinical hypothyroidism have been common diseases in the adult general population. There has been an increased recognition that more attention needs to be paid to this area since two diseases affect each other according to studies. Moreover, there has been lacking data in guidelines and study results on SCH and diabetes complications. Triglyceride indexes and thermogenic indexes have been valuable to demonstrate diabetes control levels and complications risk. Therefore we aimed to investigate the effect of SCH on these indexes in patients with type 2 Diabetes Mellitus.* ***Methods:*** *315 (after exclusion criteria 299) type 2 diabetes patients and 92 healthy controls, matched for age and sex were enrolled in the study. Patients were divided into two groups according to SCH co-occurrence. Waist circumference, Plasma glucose, lipid profile, and Urinary Albumin-Creatinine Ratio (UACR) was compared between groups. TyG, TyG-Body Mass Index, TyG-Waist Circumference, and AIP were calculated to compare the two groups.* ***Results:*** *SCH frequency was 14.1% (13/92) in healthy subjects and 10.6% (32/298) in type 2 diabetes patients (p=0.377). TG levels were higher in T2DM patients with SCH (208.0 ± 91.4 vs 169.83 ± 78.4 mg/dl, p=0.03) UACR was found significantly higher in T2DM patients with SCH (p<0.05). WC, FPG, and HbA1c were not found associated with TSH levels (p=0.41, p=0.42, p=0.22, accordingly) Urine Albumin Creatinine Ratio was found associated with Thyroid Stimulating Hormone (p=0.03). TyG-Body Mass Index, TyG-Waist Circumference and Adaptive Internet Protocol were found to increase in the SCH group (p<0.01 in three groups).* ***Conclusions:*** *According to current results, SCH was found not infrequently in patients with T2DM, additionally hypertriglyceridemia and microalbuminuria tend to be higher in patients with diabetes mellitus and coexisting SCH. As well as TyG-Body Mass Index, TyG-Waist Circumference and Adaptive Internet Protocol were found to increase in the SCH group. TyG index was shown to be associated with poorer glucose control Therefore the overlap of these two clinical situations could facilitate life threatening comorbidities.*

Keywords: Diabetes, Hypothyroidism, Microalbuminuria, Atherogenic index of plasma, Triglyceride and Glucose index

INTRODUCTION

Thyroid dysfunction and diabetes mellitus are increasingly common in the adult population. These two diseases systematically affect the human body and have consequences on metabolism. Therefore, the coincidence of these two diseases should raise additional health issues.

Hypothyroidism can occur in the adult population in the form of subclinical and overt hypothyroidism, and the prevalence of hypothyroidism varies according to iodine supply status throughout the world [1]. In the study of USA NHANES III, hypothyroidism was found to be 4.6%, while Subclinical Hypothyroidism (SCH) accounts for a larger proportion, representing up to 10% of the normal population [2,3]. SCH, according to a meta-analysis in diabetes patients could be linked to increased prevalence of diabetic complications which could sharpen disease duration and fate, however, multiple mechanisms should be suggested and how SCH effects in T2DM has not been elucidated [4].

The Triglyceride Glucose Index (TyG), a formulation of triglycerides and Fasting Plasma Glucose (FPG), is a new tool related to insulin resistance, atherosclerosis and arterial stiffness, also TyG has been found to correlate with HBA1c and insülin resistance in 155 T2DM patients [5-7]. Additionally, parameters related to TyG as a product of TyG and Waist Circumference (TyG-WC), and TyG and Body Mass Index (TyG-BMI) improve the identification of people with IR. TyG-BMI was found to be superior to HOMA-IR to demonstrate Non Alcoholic Steato-Hepatosteatosis (NASH) Atherogenic Index of Plasma (AIP), a good surrogate marker for sdLDL, was reported to be a superior predictor of cardiovascular disease to conventional lipid parameters in SCH [8,9].

METHODS

299 patients aged between 18-65 with T2DM and 92 age and gender matched healthy patients were included in the study. These patients were followed regularly at the endocrinology clinic of Istanbul Research and Education Hospital. Diabetes duration, hypertension, and hyperlipidemia were obtained from the patients' records. After 12 hours of fasting morning blood glucose, creatinine, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, thyroid function tests anti-thyroid antibodies were measured in the same laboratory. SCH was diagnosed with TSH>4 μU/ml -10 μU/ml and normal free T3 and T4 [10].

Indices were calculated according to formula in paranthesis. TyG index Ln[TG(mg/dL) × fasting glucose (mg/dL)/2], TyG-BMI=TyG index × BMI, TyG-WC=TyG index × WC, AIP=log (TG(mg/dl)/HDL-c (mg/dl) [11-14].

Inclusion Criteria

Aged 18-65, previously diagnosed T2DM patients

Exclusion Criteria

Patients with renal, hepatic failure, sepsis, pregnancy, any disease causing thyroid dysfunction, clinical hypothyroidism, or thyrotoxicosis.

After exclusion criteria, 298 patients were eligible for the study.

Written informed consent was obtained from all patients and control subjects in the study. Ethical approval was obtained from Istanbul Research and Education Hospital (2020/2436). The Declaration of Helsinki Guidelines was obeyed.

STATISTICS

Statistical analyses were performed using IBM SPSS 22.0 (Statistical Package for the Social Sciences Software Version 22.0, Inc., Chicago, IL, USA). Descriptive analyses were expressed as median (min-max) or Mean ± Standard Deviation (SD) and percentages (%), and the Shapiro-Wilk test was used for normality. For categorical variables, the Chi-square test or Fisher's exact test was used when appropriate. The student's t-test was used for the comparison of normally distributed continuous variables of two groups. The Mann-Whitney U test was used for comparisons of normally distributed continuous variables between two groups.

Logarithmic transformation was used for continuous variables that were not normally distributed. Spearman correlations were performed to examine the relationship between different variables.

RESULTS

The frequency of SCH was 14.1% (13/92) in healthy subjects and 10.6% (25/235) in patients with type 2 diabetes (p=0.377). T2DM subjects had higher BG, HbA1c, LDL and Urine Albumin-to-Creatinine ratios when compared with healthy controls ($p<0.05$, $p<0.05$, $p<0.01$, respectively) (Table 1). Tough higher, no statistically significant difference

was found in FBG, LDL and WC values between T2DM patients with SCH and without SCH patients (p=0.36, and p=0.26, p=0.45 respectively, Table 2). Mean TG levels were higher in T2DM patients with SCH (208.0 ± 91.4 *vs* 169.83 ± 78.4 mg/dl, Table 2 p=0.03). Urine Albumin-to-Creatinine Ratio was significantly higher in SCH T2DM patients (41.2 ± 85.2 *vs* 31.9 ± 48.3 mg/g, Table 2, p<0.05). WC, FPG, and HbA1c was not found associated with TSH levels (p=0.41, p=0.42, p=0.22, respectively) TG and Urine Albumin-to-Creatinine Ratio were found associated with TSH (Table 3, p<0.05) TyGBMI, TyG-WC and AIP were found increased in SCH group (p<0.01 in three groups).

Table 1 General property of study groups

	T2DM (n=298)	Control (n=92)	p-value
Age (median,min-max)	52 (21-65)	51 (20-64)	0.54
Gender (Male/Female)	119/116	49/43	0.19
Blood Glucose (mg/dl) (mean ± SD)	190.11 ± 93.42	94.78 ± 12.15	**<0.05**
HbA1c%	5.01 ± 0.22	8.91 ± 2.74	**<0.05**
LDL (mg/dl)	122.47 ± 37.88	128.96 ± 43.79	0.05
UACR	7.62 ± 12.1	52.41 ± 118.2	**<0.01**
Significant values were expressed in bold. UACR: Urine Albumine Creatinine Ratio			

Table 2 Comprasion of T2DM Subjects with/without sub clinic hypothyroidism

	Euthyroid (n=266)	SCH (n=32)	p-value
Diabetes Duration	9.46 ± 8.07	10.47 ± 7.02	0.76
FBG mg/dl	193.0 ± 89.7	207.5 ± 121.6	0.36
HbA1C%	9.1 ± 2.1	9.9 ± 2.1	0.07
TG (mg/dl)	169.83 ± 78.4	208.0 ± 91.4	**0.03**
HDL (mg/dl)	46.72 ± 37.5	44.99 ± 16.0	0.49
LDL mg/dl	128.9 ± 43.9	130.7 ± 44.4	0.26
WC (cm)	102.5 ± 15.7	104.5 ± 17.6	0.45
Body Weight (kg)	88.3 ± 17.7	92.1 ± 18.9	0.29
UACR (mg/g)	31.9 ± 48.3	41.2 ± 85.2	**<0.01**
TSH (mIU/L)	1.9 ± 0.9	6.8 ± 3.1	**<0.01**
Anti TPO (IU/ml)	26.1 ± 39.1	160.0 ± 320.1	**<0.01**
FBG:Fasting blood glucose, UACR: Urine Albumine Creatinine Ratio, TG: triglyceride Significant values were expressed in bold			

Table 3 Correlation analysis between TSH and other variables in T2DM subjects

	r	p
WC (cm)	0.062	0.424
FBG (mg/dl)	0.044	0.418
HbA1c%	0.051	0.221
UACR (mg/g)	0.114	**0.029**
TG (mg/dl)	0.221	**0.002**
FBG: Fasting blood glucose, WC: Waist Circumference, UACR: Urine Albumine Creatinine, TG: triglyceride Ratio, Significant values were expressed in bold.		

DISCUSSION

Our data showed that SCH was not uncommon in Turkish patients with type 2 diabetes, TG level and higher TyG, TyGBMI, TyGWC and AIP in patients with diabetes mellitus and SCH. These results suggest that screening for

subclinical hypothyroidism could be an important issue and target to evaluate and slow down complications, which could be considered an important risk factor for life-threatening complications in diabetic patients (Table 4).

Table 4 Subclinical hypothyroidism and triglyceride indexes and adaptive internet protocol

	SCH (+) (n=32	SCH (-) (n=266)	p
TyG	8.91 ± 0.51	9.18 ± 0.53	0.13
TyBMI	268.90 ± 60.55	354.61 ± 70.69	**0.001**
TyGWC	881.33 ± 131.40	1030.88 ± 230.05	**0.005**
AIP	1.09 ± 0.62	1.54 ± 0.56	**0**
TyG: triglyceride glucose index, TyBMI: TyG and Body Mass İndex, TyGWC: TyG and Waist Circumference, AIP: Atherogenic Index of Plasma			

Subclinical hypothyroidism alone is an independent risk factor for increased mortality, cardiovascular or otherwise [15]. Asvold, et al. found that SCH caused increased creatinine levels and decreased glomerular function in a cross-sectional study of undiagnosed thyroid disease and a population over 40 years of age [16]. Several mechanisms are likely responsible for this association. First, SCH contributes to poor glycemic status in diabetic patients [17]. Endothelial dysfunction could be triggered by SCH and lead to increased capillary basement membrane thickness [18]. Patients with overt and subclinical hypothyroidism, already known as an important risk factor for atherosclerosis, have been found to have increased endothelial dysfunction and carotid intima-media thickness [19] (Table 5).

Table 5 Poor glucose control group

	HbA1C<8.5%	HbA1C ≥ 8.5%	p
TyG	8.92 ± 0.47	9.93 ± 0.44	**<0.01**
TyBMI	277.98 ± 54.92	290.91 ± 64.89	0.25
TyGWC	933.54 ± 181.15	943.18 ± 128.61	0.73
AIP	1.10 ± 0.62	1.24 ± 0.64	0.09
TyG: triglyceride glucose index, TyBMI: TyG and body mass index, TyGWC TyG: and waist circumference, AIP: Atherogenic Index of Plasma			

According to studies, hypothyroidism may lead to worsening glomerular function due to increased vascular resistance and decreased cardiac output. In a study of 239 patients with SCH, uric acid and creatinine levels tended to be higher compared with euthyroid patients [20]. On the other hand, treatment with L-thyroxine increased flow-mediated dilation but did not decrease carotid intima-media thickness, according to a meta-analysis of 541 SCH patients [21].

We have found TyG index is higher with poorer glycemic control, likewise a study from China found TyG index to assess glycemic status in T2DM patients however, we couldn't find in SCH patients a significantly increased TyG index. Highest association was found with AIP which was found associated with an increased risk of hypertension, decreased GFR and increased body fat level.

CONCLUSION

Conclusion: According to current results, SCH was found not infrequently in patients with T2DM, additionally hypertriglyceridemia and microalbuminuria tend to be higher in patients with diabetes mellitus and coexisting SCH. The overlap of these two clinical situations could facilitate life threatening comorbidities. As well as TyGBMI, TyG-WC and AIP were found to increase in the SCH group. TyG index was shown to be associated with poorer glucose control. Further studies are needed to clarify the mechanism for this association, and new measures for thyroid function situation should be taken to prevent more clinical dangerous complications.

DECLARATIONS

Conflict of Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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