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Original Article

Relationship between serum thyroid stimulating hormone levels and severity of coronary artery lesions in elderly patients with type 2 diabetes mellitus

Fu Wang[1*], Yuxia Jing[2*], Jinhua Zhao[3], Qiaoyi Wang[4], Lei Wang[5]

[1]Department of Endocrinology, Jinxiang People's Hospital Affiliated to Jining Medical University, Jining, Shandong Province, China; [2]Department of Geriatrics, Tianjin Fifth Central Hospital, Tianjin, China; [3]Department of Endocrinology, The People's Hospital of Chiping District, Liaocheng, Shandong Province, China; [4]Department of Emergency, Weifang Traditional Chinese Medicine Hospital, Weifang, Shandong Province, China; [5]Department of Endocrinology, Laiyang Central Hospital of Yantai, Yantai, Shandong Province, China. [*]Equal contributors and co-first authors.

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Abstract: Objective: The aim of the current study was to explore the relationship between serum thyroid stimulating hormone levels and severity of coronary artery lesions in elderly patients with type 2 diabetes mellitus (T2DM). Methods: This retrospective study was conducted with 105 elderly T2DM patients and 60 healthy subjects. The relationship between serum thyroid stimulating hormone (TSH) levels and severity of coronary heart disease (CHD), as well as severity levels of coronary artery stenosis, was analyzed. Results: Serum TSH levels in the CHD group were significantly higher than those in the non-CHD group (P<0.001). Additionally, serum TSH levels in the non-CHD group were significantly higher than those in the control group. There was a positive correlation between serum TSH levels and severity of coronary artery stenosis (r=0.358, P=0.031). Serum TSH levels in the single-vessel lesion group were lower than those in both two-vessel and three-vessel lesion groups. Moreover, serum TSH levels in the two-vessel lesion group were lower than those in the three-vessel lesion group (all P<0.001). Serum TSH levels in the stable angina pectoris group were lower than those in both the non-ST and ST segment elevation myocardial infarction groups. Similarly, serum TSH levels in the unstable angina pectoris group were lower than those in both the non-ST and ST segment elevation myocardial infarction groups (all P<0.001). Gensini scores were positively correlated with serum TSH levels (r=0.6444, P<0.001). Conclusion: Serum TSH levels can be used to predict the risk of coronary artery lesions in elderly T2DM patients. Thus, they are worthy of further clinical research.

Keywords: Type 2 diabetes, thyroid stimulating hormone, coronary heart disease, correlation

Introduction

With accelerated aging, incidence of type 2 diabetes mellitus (T2DM) in elderly patients has increased yearly. It has been reported that there could be 615 million T2DM patients by 2040 and that the prevalence of diabetes in China could be 11% [1, 2]. T2DM patients are more susceptible to thyroid disease, due to various reasons [3]. In clinical practice, hypothyroidism is a common thyroid disease. Increased thyroid stimulating hormone (TSH) levels, defined as subclinical hypothyroidism, are often observed in T2DM patients [4]. In turn, hypothyroidism can change glucose metabolism and induce insulin resistance, leading to fluctuating and uncontrolled blood sugar levels [5, 6]. Gu et al. reported that the prevalence of diabetes was closely related to TSH levels [7].

T2DM is an independent risk factor for occurrence and development of coronary heart disease (CHD) [8]. Results of recent studies have suggested that TSH levels are related to various metabolisms, including lipid metabolism and bone metabolism [9, 10]. Furthermore, TSH levels have been associated with occurrence of cardiovascular adverse events and, to a certain extent, with severity of atherosclerosis [11]. Serum TSH levels have been closely related to occurrence of CHD in T2DM patients [12]. However, there is no evident correlation between TSH levels and other health problems

[13]. In addition, there is no correlation between TSH levels and severity of coronary artery lesions [14]. Thus, the relationship between serum TSH levels and severity of coronary artery lesions in elderly T2DM patients remains controversial. The present study explored the relationship between serum TSH levels and severity of coronary artery lesions in elderly T2DM patients.

Materials and methods

General information

A total of 60 healthy subjects (control group) and 105 elderly T2DM patients (T2DM group), admitted to the Department of Endocrinology in Laiyang Central Hospital of Yantai, from June 2018 to December 2018, were enrolled in this retrospective study. Patients in the experimental group were between 60-80 years old, with an average age of 69.5±8.2 years old. Subjects in the control group had a mean age of 67.2±7.6 years old.

The present study was approved by the Ethics Committee of Laiyang Central Hospital of Yantai and informed consent was obtained for all patients.

Inclusion and exclusion criteria

Inclusion criteria: Patients diagnosed with T2DM for more than 6 months [15]; Patients over 60 years old; Patients with normal thyroid function.

Exclusion criteria: Patients with incomplete medical records; Patients with severe malnutrition, tumors, and other diseases; Patients with mental or cerebrovascular disease; Patients with thyroid disease; Patients using drugs influencing thyroid function.

Grouping

Diagnostic criteria and classifications of CHD were based on standards established by the Cardiovascular Branch of the Chinese Medical Association in 2007 [16]. T2DM was diagnosed according to the diagnostic criteria of diabetes mellitus [17]. In this study, 30 elderly T2DM patients without CHD were allocated to the non-CHD group. At the same time, 75 elderly T2DM patients combined with CHD were assigned to the CHD group. According to the severity of coronary artery stenosis, 105 patients were classified into four groups, including stenosis below 30% group, stenosis between 31-49% group, stenosis between 50-69% group, and stenosis over 70% group [18]. According to angiographic results of patients in the CHD group, patients were further divided into three groups, including the single-vessel lesion group (37 patients), double-vessel lesion group (27 patients), and three-vessel lesion group (11 patients). Moreover, 75 elderly T2DM patients combined with CHD were divided into the stable angina pectoris group (25 patients), unstable angina pectoris group (20 patients), non-ST segment elevation myocardial infarction group (17 patients), and ST segment elevation myocardial infarction group (13 patients), based on different diagnostic criteria of CHD.

Methods

Fasting venous blood (5 mL) of patients enrolled was collected at 8:00 a.m. before and one month after treatment. Blood samples were preserved in a sterile tube supplied with ethylenediaminetetraacetic acid and stored at 4°C. After 15 minutes, serum was harvested by centrifugation at a speed of 3,300 rpm. Subsequently, 40 μL of protease inhibitor dissolved in phosphate buffer solution was added and stored at -80°C. A serum enzyme-linked immunosorbent assay kit (Shanghai Hengyuan Bio Co., Ltd., China) was applied to detect serum TSH levels. Results were collected using a fully automatic microplate reader (Multiscan MK3, Thermo Fisher Scientific, USA).

Coronary angiography: X-ray digital subtraction angiography (INNOVA3100, GE Healthcare, UK) was applied for puncture angiography on radial arteries. Results were scored using the Gensini coronary scoring system [19].

Statistical methods

Data was analyzed using SPSS statistical software version 22.0. Measurement data are expressed as mean ± standard deviation ($\bar{x}$ ± sd). For data with normal distribution and homogeneity, paired t-tests were applied for before-after comparisons within the same group. Otherwise, rank-sum tests were used for inner-group comparisons. Regarding multiple comparisons, one-way analysis of variance (ANOVA) was adopted. Bonferroni's post hoc tests were applied for pairwise comparisons

Table 1. Comparison of basic data

Group	Control group	Non-CHD group	CHD group	χ^2/F value	*P* value
Gender (n)				0.440	0.803
Male	32	18	40		
Female	28	12	35		
Age (years)	67.3±7.6	66.8±9.5	67.4±7.6	0.927	0.398
Systolic blood pressure (mmHg)	136.83±7.65	137.84±8.10	138.93±7.23	0.763	0.452
Diastolic blood pressure (mmHg)	87.50±5.09	86.84±8.10	86.01±6.98	0.892	0.412
Triglyceride (mM)	1.14±0.69	1.79±0.66	1.79±0.66	17.542	<0.001
Total cholesterol (mM)	4.56±0.44	5.86±0.44	5.86±0.44	168.493	<0.001
Low density lipoprotein (mM)	1.52±0.44	1.05±0.34	1.12±0.34	23.237	<0.001
High density lipoprotein (mM)	2.42±0.42	3.82±0.87	3.82±0.86	69.644	<0.001
BMI (kg/m^2)	26.72±1.96	26.99±2.03	27.27±2.13	0.769	0.465
Blood glucose (mM)	5.88±2.43	10.99±4.66	10.87±4.65	24.982	<0.001
Glycated hemoglobin (%)	4.91±1.24	8.23±3.23	8.32±3.62	31.232	<0.001

Note: BMI, body mass index.

Table 2. Comparison of serum TSH levels in the three groups

Group	Number of patients	Serum TSH level (mIU/L)
Control group	60	2.64±0.48
Non-CHD group	30	3.65±1.56*
CHD group	75	5.57±3.19$^{***,\#\#\#}$
F value		28.711
P value		<0.001

Note: Compared with the control group, *P<0.05, ***P<0.001; compared with the non-CHD group, $^{\#\#\#}$P<0.001.

between the means when ANOVA was significant. Pearson's product-moment correlation analysis was used to analyze the linear correlation between two variables (there was a correlation between two variables when the r value was over 0.01). Differences are statistically significant when *P*-values<0.05.

Results

Basic data

As displayed in **Table 1**, there were no significant differences concerning gender, age, systolic blood pressure, diastolic blood pressure, and body mass index (BMI) between the three groups (all P>0.05). However, there were significant differences concerning triglycerides, total cholesterol, low density lipoprotein, high density lipoprotein, blood glucose, and glycated hemoglobin between the three groups (all P<0.001).

Serum TSH levels in the three groups

As shown in **Table 2**, serum TSH levels in the CHD group were significantly higher than those in the non-CHD group (P<0.001). Serum TSH levels in the non-CHD group were significantly higher than those in the control group (P<0.05).

Serum TSH levels in T2DM patients with different severities of coronary artery stenosis

As displayed in **Table 3**, serum TSH levels in the group of stenosis below 30% were lower than those in both stenosis between 50-69% and stenosis over 70% groups (both P<0.05). Serum TSH levels in the group of stenosis between 31-49% were lower than those in both stenosis between 50-69%, and stenosis over 70% groups (both P<0.05). There was a positive correlation between serum TSH levels and severity of coronary artery stenosis (r=0.358, P=0.031).

Serum TSH levels in T2DM patients with different severities of coronary artery lesions

Serum TSH levels in the single-vessel lesion group were lower than those in both two-vessel and three-vessel lesion groups. Moreover, serum TSH levels in the two-vessel lesion group were lower than those in the three-vessel lesion group (all P<0.001, **Table 4**).

Serum TSH levels in T2DM patients with different CHD

Serum TSH levels in the stable angina pectoris group were lower than those in both the non-ST

Table 3. Comparison of serum TSH levels in T2DM patients with different severities of coronary artery stenosis

Group	Number of patients	Serum TSH level (mIU/L)
Stenosis below 30%	16	3.59±1.56
Stenosis between 31-49%	14	3.72±1.61
Stenosis between 50-69%	45	5.29±1.45$^{*,\#}$
Stenosis over 70%	30	6.57±4.21$^{***,\#\#,\dagger}$
F value		6.416
P value		0.001

Note: Compared with the stenosis below 30% group, *P<0.05, ***P<0.001; compared with the stenosis between 31-49% group, $^{\#}$P<0.05, $^{\#\#}$P<0.01. compared with the stenosis between 50-69% group, †P<0.05.

Table 4. Comparison of serum TSH levels in T2DM patients with different severities of coronary artery lesions

Group	Number of patients	Serum TSH level (mIU/L)
Single-vessel lesion	37	3.81±1.56
Double-vessel lesion	27	5.79±1.52***
Three-vessel lesion	11	10.92±4.11$^{***\#\#\#}$
F value		48.979
P value		0.001

Note: Compared with the single-vessel lesion group, ***P<0.001; compared with the double-vessel lesion group, $^{\#\#\#}$P<0.001.

and ST segment elevation myocardial infarction groups. Similarly, serum TSH levels in the unstable angina pectoris group were lower than those in both the non-ST and ST segment elevation myocardial infarction groups (all P<0.001, **Table 5**).

Correlation between Gensini scores and serum TSH levels

As illustrated in **Figure 1**, Gensini scores were positively correlated to serum TSH levels (r=0.6444, P<0.001).

Discussion

TSH levels are closely related to blood glucose levels. Long-term high blood glucose levels in patients with diabetes may lead to chronic hypoxia in tissues and production of acidic substances, inhibiting the activity of deiodinase. This makes the conversion of thyroxine constrained, resulting in increased TSH levels [20]. Results of another study also indicated that it is easier to induce oxidative stress, produce pro-inflammatory factors, and inhibit deiodinase activity under hyperglycemia, making TSH levels change [21]. As a disease tightly associated with CHD, T2DM is an independent risk factor for occurrence and development of CHD [8]. However, CHD is not observed in all T2DM patients. In addition, TSH levels in T2DM patients are different. The present study found that serum TSH levels in elderly T2DM patients were significantly higher than those in healthy subjects.

Subclinical hypothyroidism is defined as an increase in TSH levels, but without clinical symptoms. For patients with subclinical hypothyroidism, serum thyroid hormone levels are normal and only TSH levels are elevated. However, it has been found that incidence rates of cardiovascular diseases in patients with subclinical hypothyroidism were significantly increased [22]. Results of recent studies have shown that elevated TSH levels could raise the risk of atherosclerosis [23, 24]. Furthermore, it has been suggested that TSH levels could influence blood lipid metabolism. To be specific, cholesterol, triglycerides, and low-density lipoproteins levels are enhanced as a result of high TSH levels, increasing the risk of atherosclerosis [25]. In summary, occurrence and development of coronary artery lesions are caused by various factors, including blood lipid metabolism, inflammatory response, vascular endothelial function, coagulation function, and the fibrinolytic system. These factors are correlated to elevated TSH levels. The current study found that greater severity of coronary artery stenosis correlated with higher serum TSH levels. Moreover, a greater number of lesions correlated with higher serum TSH levels. Results suggest a correlation between serum TSH levels and atherosclerosis.

Patients with subclinical hypothyroidism are more prone to coronary spasms and cardiovascular disease [26]. There is a correlation between coronary spasms and TSH levels. High TSH levels can promote the production of inflammatory factors, associated with oxidative stress. Consequently, damage of endothelial function is aggravated and coronary spasms are developed [27]. Auer et al. confirmed CHD of 100 patients with normal thyroid function

Table 5. Comparison of serum TSH levels in T2DM patients with different CHD

Group	Number of patients	Serum TSH level (mIU/L)
Stable angina pectoris group	25	3.88±1.60
Unstable angina pectoris group	20	3.96±1.46
Non-ST segment elevation myocardial infarction group	17	7.98±3.54***,###
ST segment elevation myocardial infarction group	13	8.12±3.40***,###
F value	-	16.409
P value	-	<0.001

Note: Compared with the stable angina pectoris group, ***P<0.001; compared with the unstable angina pectoris group, ###P<0.001.

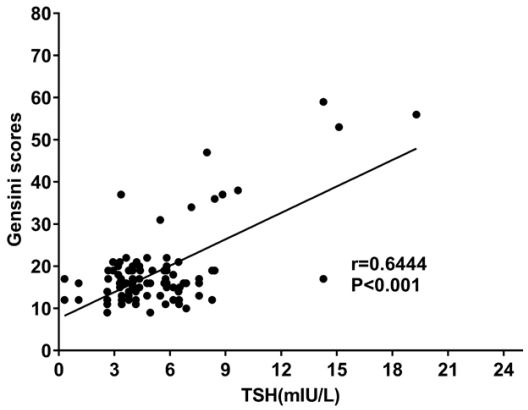

Figure 1. Correlation between Gensini scores and serum TSH levels. TSH, thyroid stimulating hormone.

using coronary angiography. They found that TSH levels were related to the prevalence of CHD [28]. In the current study, serum TSH levels in elderly T2DM patients combined with myocardial infarction were significantly higher than those in T2DM patients accompanied by angina pectoris. This might be related to cardiovascular disease induced by high serum TSH levels. Gensini scores are often used to evaluate the severity of coronary artery lesions [29]. The present study found that Gensini scores were positively correlated with serum TSH levels, suggesting that the severity of coronary artery lesions is positively correlated to serum TSH levels.

However, the number of patients in the current study was inadequate. As a retrospective study, it was influenced by many factors. Therefore, a multi-center prospective study with an expanded sample size is necessary to verify present conclusions.

In conclusion, serum TSH levels may be used to predict the risk of coronary artery lesions in elderly T2DM patients. Therefore, serum TSH levels are worthy of further clinical research.

Disclosure of conflict of interest

None.

Address correspondence to: Lei Wang, Department of Endocrinology, Laiyang Central Hospital of Yantai, No. 111 Changshan Road, Yantai 265200, Shandong Province, China. Tel: +86-0535-7226121; E-mail: wangleily1y@163.com

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