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A high thyroid stimulating hormone level is associated with diabetic peripheral neuropathy in type 2 diabetes patients

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ABSTRACT

Aim: The association between thyroid stimulating hormone (TSH) and type 2 diabetes mellitus (T2DM) is well known. However, whether TSH is related to diabetic peripheral neuropathy (DPN) has not been studied. The aim of this study was to explore the relationship between TSH and DPN in Chinese patients with T2DM.

Methods: In this cross-sectional study, 605 patients with T2DM were enrolled. Subclinical hypothyroidism (SCH) was defined as an elevated TSH level (>4.0 mIU/L) and a normal free thyroxine level. DPN was evaluated by neurological symptoms, neurological signs, and electromyogram.

Results: Serum TSH levels were significantly higher in DPN and signs of DPN compared with non-DPN T2DM patients (both $P < 0.01$).The prevalence of DPN and signs of DPN in SCH subjects was higher than that in euthyroid subjects (both $P < 0.01$). Spearman's correlation analysis showed that the serum TSH level was positively associated with DPN ($r = 0.172$, $P < 0.01$). A significant independent association between TSH and DPN was found by multiple logistic regression analysis after adjusting for potential confounding variables [odds ratio (OR) = 1.365, $P < 0.01$]. The patients were sequentially assigned to quartiles according to TSH level. Compared with quartile 1, patients in quartile 2 ($P < 0.01$), quartile 3 ($P = 0.01$), and quartile 4 ($P < 0.01$) had a higher risk of DPN. Receiver-operating characteristic curve analysis revealed that the optimal cutoff point of TSH to indicate DPN was 3.045 mIU/L in men and 2.94 mIU/L in women.

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Abbreviations: AUC, area under the curve; BP, blood pressure; CVD, cardiovascular disease; CI, confidence interval; DN, diabetic nephropathy; DP, diastolic pressure; DPN, diabetic peripheral neuropathy; DR, diabetic retinopathy; $1,25(OH)_2D_3$, 1,25-dihydroxyvitamin D_3; FT3, free triiodothyronine; FT4, free thyroxine; GA, glycated albumin; HbA1c, glycosylated hemoglobin; IR, insulin resistance; NCV, nerve conduction velocity; OR, odds ratio; PAD, peripheral arterial disease; ROC, receiver-operating characteristic curve; SCH, subclinical hypothyroidism; T2DM, type 2 diabetes mellitus; TSH, thyroid stimulating hormone; UA, uric acid.

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Conclusion: TSH level is independently associated with DPN in Chinese population with T2DM. A high serum TSH level may be a potential risk factor for DPN.

1. Introduction

Diabetic peripheral neuropathy (DPN) is a common complication of longstanding diabetes mellitus that affects up to 50% of diabetic patients [1] and can cause considerable morbidity in many patients, resulting in inadequate proprioceptive feedback, impaired postural balance, and a higher fall risk, thus leading to a deterioration of their quality of life. Previously reported relevant factors that have been identified for the development of DPN include hyperglycemia, dyslipidemia, smoking [2], vitamin D deficiency [3,4], and cystatin C [5]. Moreover, it has also been proved that vascular diseases including cardiovascular disease (CVD), peripheral arterial disease (PAD), diabetic nephropathy (DN), and diabetic retinopathy (DR) were also closely related to DPN [2,6].

Subclinical hypothyroidism (SCH), which affects 4–10% of the general population [7] and 4–17% of the population with diabetes [8], is defined as an asymptomatic state that is characterized by an elevated serum concentration of thyroid-stimulating hormone (TSH) and normal serum free thyroxine (FT4) [9]. SCH has been reported to be correlated with DN [10,11], DR [12–14], and CVD [15] in patients with type 2 diabetes mellitus (T2DM). Recently, a systematic review and meta-analysis revealed that SCH might affect the development of DPN with an overall odds ratio (OR) of 1.87 [16].

However, to our knowledge, the relationship between serum TSH and DPN has not been described in Chinese T2DM patients. Owing to the paucity of data regarding the potential association of TSH with DPN, the aim of this study was to clarify the possible link between TSH and DPN in Chinese patients with T2DM.

2. Subjects and methods

2.1. Study population

We recruited 605 Chinese patients (353 women and 252 men) with previously diagnosed T2DM at the Shanghai Clinical Medical Center of Diabetes from January 2011 to December 2013. The diagnostic criteria of T2DM were based on American Diabetes Association standards [17]. SCH was defined as an elevated TSH level (>4.0 mIU/L) and a normal FT4 level (12–22 mIU/L). Exclusion criteria included a history of thyroid disease with or without treatment, acute complications of diabetes, history of hypothalamus or pituitary diseases, history of cerebral infarction, serious liver or renal dysfunction, alcoholism, vitamin B12 deficiency, malignant tumors and complicated with degenerative changes in lumbar or cervical spine.

2.2. Data collection

Demographic and anthropometric parameters, including diabetes duration, alcohol consumption, daily number of cigarettes smoked, hypertension history, and history of other diseases, were collected in the hospital using a standardized questionnaire. Venous blood was drawn from all patients after an overnight fast to measure the following laboratory parameters: fasting plasma glucose, C-peptide, total cholesterol, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, glycosylated hemoglobin (HbA1c), glycated albumin (GA), serum creatinine, uric acid, C-reactive protein, 1,25-dihydroxyvitamin D3 [1,25(OH)2D3], free triiodothyronine (FT3), FT4, and TSH levels. Urine samples were collected to measure 24-h urinary albumin levels. Height, body weight, and blood pressure (BP) were measured at the same time on a standardized form by the same physician. BP was measured in the sitting position after a rest period of more than 5 min. Hypertension was defined as a systolic BP >140 mmHg and/or a diastolic BP >90 mmHg.

Serum TSH concentration was determined using a chemiluminescence immunoassay (Roche Cobas 6000; Roche Ltd., Basel, Switzerland). Lipid profiles and blood urea nitrogen, creatinine, and uric acid concentrations were analyzed by standard enzymatic procedures on an automated bioanalyzer (7600-020; Hitachi, Tokyo, Japan). Plasma glucose was measured using the Glamour 2000 autoanalyzer (Molecular Devices, Sunnyvale, CA, USA) and the glucose oxidase method (Glucose Kit; Shanghai Kehua Bio-engineering, Shanghai, China). HbA1c was estimated using high-performance liquid chromatography (Bio-Rad Variant II; Bio-Rad Laboratories, Hercules, CA, USA). The GA value was determined using an enzyme-based assay (Lucica GA-L; Asahi Kasei Pharma, Tokyo, Japan) and the Glamour 2000 autoanalyzer. Body mass index was calculated as body weight (kg) divided by the square of height (m).

DPN was categorized as follows: (1) DPN, clinically evident DPN (defined as at least two positive findings among sensory symptoms, signs, and reflex abnormalities consistent with a distal symmetrical polyneuropathy) and abnormal results on nerve conduction tests (defined by the presence of at least one abnormal nerve attribute of amplitude, latency, F-wave, or nerve conduction velocity in two or more nerves among the median, peroneal, and sural nerves); (2) signs of DPN, clinically evident DPN or abnormal results on nerve conduction tests; and (3) non-DPN, neither clinically evident DPN nor abnormal nerve conduction tests [18].

2.2.1. Neurological symptoms and signs

The assessment of neurological symptoms and signs was based on the Toronto Clinical Scoring System [19]. Any pain,