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Association between sub-clinical hypothyroidism and heart failure with preserved ejection fraction

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With the acceleration of aging across the globe, it is expected that heart failure with preserved ejection fraction (HFpEF) may become more prevalent in the next 10 years worldwide. Thyroid hormones have been proven to influence physiologic functions of the cardiovascular system in various ways. Approximately 22% of patients with HFpEF had been demonstrated to have thyroid dysfunction.[1] Clinical studies have confirmed that patients with sub-clinical hypothyroidism (SCH) had a higher risk of cardiovascular diseases perhaps due to increased low-density lipoprotein, elevated homocysteine (Hcy), and hyper-coagulative blood.[2] Interestingly, a previous animal study showed that SCH may lead to the accumulation of mucopolysaccharides in the myocardium, potentially leading to heart failure,[3] suggesting that SCH may adversely affect cardiac function. However, to the best of our knowledge, clinical studies that aim to evaluate the influence of thyroid hormones in patients with HFpEF are rare. Therefore, in this pilot study, we aim to evaluate the association between SCH and HFpEF, and to explore its clinical significance.

This study included patients with HFpEF who were admitted to the Department of Cardiology of Lanzhou University Second Hospital between January 1, 2016, and January 1, 2018. The diagnostic criteria for HFpEF were in accordance with the *2016 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure*. The research protocol was approved by the Ethics Committee of Lanzhou University Second Hospital before the performance of the study. All patients signed the informed consent before enrollment. The HFpEF patients with SCH were considered as the observation group ($n = 73$). Other patients with HFpEF who had normal thyroid function in our hospital in the same period were selected as the control group ($n = 73$). Two groups were matched by age, gender, and index year. The definition of SCH is mainly based on serologic indices: higher thyroid-stimulating hormone (TSH), but normal free tri-iodothyronine (FT3) and free thyroxine (FT4). Patients were included if they fulfilled the following criteria: (1) confirmed diagnosis of HFpEF; (2) with typical symptoms or signs of heart failure; (3) with left ventricular ejection fraction (LVEF) ≥50%; (4) with cardiac function of II to III as evaluated by the New York Heart Association (NYHA) heart failure classification; (5) with the results of baseline thyroid function tests; and (6) no recent intake of medications that might affect thyroid function. Patients were excluded if they were with the following clinical situations: (1) patients with clinical hypothyroidism, hyper-thyroidism, or a history of thyroid disease; (2) patients with systolic heart failure; (3) patients with valvular disease; (4) patients with acute myocardial infarction; (5) patients with any arrhythmia; and (6) patients with pericardial effusion.

Baseline data of each patient including gender, age, medical history, concomitant disease, medication, and other general information were obtained at admission via a predefined data table. From each patient, 3 mL of venous blood samples were obtained in the morning, after fasting overnight. Biochemical indexes including TSH, FT3, FT4, brain natriuretic peptide (BNP), and C-reactive protein (CRP) were measured with an automatic biochemical analyzer by the laboratory of Lanzhou University Second Hospital after admission to the hospital. An experienced doctor from the Department of Ultrasound of Lanzhou University Second Hospital performed echocardiographic examination on the same day of blood testing, with an HP Sonos 5500 Color Doppler Ultrasound Machine (Hewlett-Packard, Palo Alto, CA, USA). LVEF was measured by

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trans-thoracic two-dimensional echocardiography. The peak velocity of blood flow across the mitral valve in early diastole (*E*) and the peak velocity of blood flow across the mitral valve in late diastole (*A*) were measured by trans-thoracic-pulsed Doppler echocardiography and the *E*/*A* ratio was calculated. The mitral annular velocity in early diastole (*E*′) was measured by tissue Doppler imaging and the *E*/*E*′ ratio was calculated.

Continuous data were presented as mean ± standard deviation (SD), while categorical data were presented as numbers and proportions. An independent sample *t* test and a Chi-square test were used to compare the continuous and categorical data of the two groups, respectively. Pearson correlation was adopted to analyze the correlation between measurement data. We considered differences statistically significant if $P < 0.05$. Statistical analyses were performed with SPSS 12.0 (IBM Corporation, USA).

The baseline characteristics of the patients with HFpEF, according to the status of thyroid function (SCH or euthyroidism), are presented in Supplementary Table 1, http://links.lww.com/CM9/A163. Patients from the two groups were matched for baseline clinical characteristics including age, gender, body mass index, systolic blood pressure, diastolic blood pressure, comorbidities (including hypertension, coronary heart disease, and diabetes), and primary medications such as angiotensin converting enzyme inhibitors, calcium channel blockers, and statins.

Compared with HFpEF patients with euthyroidism, those with SCH had significantly increased levels of BNP (210.45 ± 52.42 *vs.* 188.75 ± 49.08 pg/mL, $P < 0.05$) and CRP (2.32 ± 0.89 *vs.* 1.26 ± 0.33 mg/L, $P < 0.05$). Moreover, results of color echocardiographic examination indicated that the *E*/*A* ratios in the SCH group were significantly lower and the *E*/*E*′ ratios in the SCH group were significantly higher than those in the euthyroidism group ($P < 0.05$), while no statistical differences in LVEF, *E* velocity, and *E*' velocity were detected between the two groups [Supplementary Table 2, http://links.lww.com/CM9/A163].

Results of Pearson correlation tests showed that circulating TSH was positively correlated with circulating levels of BNP ($r = 0.335$, $P < 0.05$), CRP ($r = 0.256$, $P < 0.05$), and the *E*/*E*′ ratio ($r = 0.266$, $P < 0.05$), but not with the *E*/*A* ratio [Supplementary Figure 1, http://links.lww.com/CM9/A164]. These results suggested that SCH may adversely affect the cardiac diastolic function in patients with HFpEF.

The cardiovascular system is a specific target of thyroid hormones. T3 combines with nuclear receptors in cells and promotes the activity of cardiac myocytes and vascular smooth muscle cells through regulating the transcription process. SCH is equivalent to early or mild hypothyroidism. A meta-analysis of prospective cohort studies indicated that a high TSH level (>10 mU/L) was associated with a higher risk of cardiovascular events and mortality.[4] As SCH and cardiovascular disease are closely related, it can be concluded that SCH, which is similar to thyroid hormone deficiency to some degree, may lead to molecular and structural disorders during the occurrence of HFpEF and have a series of impacts on the morphology and function of the myocardium, which further lead to adverse effects during the development of cardiac dysfunction.

CRP is an independent risk factor for cardiovascular events, and BNP level is an important marker of the severity of cardiac dysfunction. After thorough analysis of 75 HFpEF patients with SCH, it was found that increased BNP, CRP, and *E*/*E*′ ratio are independently correlated with SCH, which suggest that comorbidities of SCH may associate with cardiac diastolic function in patients with HFpEF. Moreover, the results of this study also showed that the *E*/*E*' ratio was significantly higher and the *E*/*A* ratio was significantly lower in the SCH group than in the euthyroidism group, indicating the further decrease of cardiac diastolic function.

Some studies have discussed the potential mechanism of the adverse influence of SCH on cardiac diastolic function. Sarco/endoplasmic reticulum Ca^{2+}-ATPase isoform 2 (SERCA2) is an important calcium transporter that is responsible for the reuptake of calcium from plasma into the sarco/endoplasmic reticulum, thereby becoming a determinant of cardiac diastolic function. SERCA2 is negatively regulated by phospholamban and research shows that thyroid hormones activate the genes encoding α-myosin heavy chain and SERCA2, thereby promoting the reuptake of calcium during cardiac diastole, and thereby further improving ventricular diastolic function.[5] However, the relative deficiency of thyroid hormones in SCH can lead to a decline in the gene encoding SERCA2, which is followed by a decrease in SERCA2 protein level, resulting in the decrease of calcium uptake and ultimately leading to impaired ventricular relaxation in cardiac diastole. However, the potential influence of SCH on the function of the SERCA2 system, despite its known associated changes in thyroid hormones, remains to be determined.

Accordingly, checking thyroid function for all newly diagnosed heart failure patients is recommended by the ACC/AHA Guidelines for the Diagnosis and Management of Heart Failure.[1] We hypothesize that the correction of SCH in patients with HFpEF may be beneficial for the diastolic cardiac function and prognosis in these patients. However, this study is a clinical observation with a limited sample size. Therefore, the results of the study should be evaluated in other studies of a larger sample size to further discuss the role of SCH in the development of HFpEF. And this will help clarify the pathogenesis of the disease and optimize clinical diagnosis and treatment.

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Conflicts of interest

None.

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