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Relationship between thyroid dysfunction and chronic kidney disease in community-dwelling older adults

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ABSTRACT

Objectives: Renal function has been shown to be influenced by thyroid status in animal models and human studies. We aimed to assess the cross-sectional association between thyroid hormones and function with prevalence of chronic kidney diseases (CKD) in older adults.
Study design: 1571 Blue Mountains Eye Study participants aged ≥60 years were analyzed in 2002–4. Thyroid dysfunction was defined using serum thyrotropin (TSH) screen, followed by serum free T4 (FT4) assessment. Baseline biochemistry including serum creatinine was measured. Moderate CKD was defined as estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2.
Results: After adjusting for age, sex, receipt of pension payment, body mass index, smoking, hypertension and diabetes, persons with any thyroid dysfunction (hyperthyroidism or hypothyroidism) had 84% higher likelihood of having CKD, odds ratio, OR, 1.84 (95% confidence intervals, CI, 1.03–3.31). Participants in the highest versus lowest quartile (reference) of serum TSH and FT4 had a significantly greater odds of prevalent CKD, OR 1.82 (95% CI 1.22–2.71), and OR 1.64 (95% CI 1.10–2.45), respectively. Similarly, among participants not receiving treatment for their thyroid dysfunction ($n = 1329$), those in the third and fourth quartiles of serum TSH had significantly greater odds of having prevalent CKD, OR 1.83 (95% CI 1.15–2.92) and OR 1.96 (95% CI 1.23–3.13), respectively, $P_{trend} = 0.001$. Significant associations were not observed between type of thyroid dysfunction (hyperthyroidism or hypothyroidism) and prevalent CKD.
Conclusions: Increasing serum TSH was associated with a greater likelihood of prevalent CKD among older adults, independent of the influence of age, diabetes and hypertension.

1. Introduction

Thyroid hormones are important for the growth and development of the kidney [1]. On the other hand, the kidney is not only an organ for metabolism and elimination of thyroid hormones, but also a target organ of some of the iodothyronines' actions [1]. Both hypothyroidism and hyperthyroidism induce changes in renal blood flow, glomerular filtration rate (GFR), tubular secretory and absorptive capacity, electrolyte pumps and kidney structure [2–4]. Thyroid dysfunction has special characteristics in those patients with advanced kidney disease [3]. Conversely, the different treatments used in the management of patients with chronic kidney disease (CKD) and thyroid dysfunction may be accompanied by changes in or adverse events on thyroid and kidney function, respectively [1].

The majority of studies investigating the effect of thyroid hormone on the kidney have been performed in rats [2]. Further, the renal effects of thyroid hormones in humans have been largely investigated in clinic-based samples, and there are a paucity of population-based data on this relationship. A Dutch study of 51 patients with thyroid dysfunction observed that there was a strong correlation between change in thyroid status and the change in renal function as a result of treatment of their dysfunction, expressed as serum creatinine ($r^2 = 0.81$, $p < 0.0001$) and estimated GFR ($r^2 = 0.69$, $p < 0.0001$) [2]. A UK clinic-based study of 2023 patients aged 18 years and over, showed that the median eGFR of hypothyroid, euthyroid and hyperthyroid patients was 64, 77 and 107 ml/min/1.73 m^2, respectively, and that all groups significantly differed from each other ($p < 0.0001$) [5]. Recently, a Norwegian population-based study of 29,480 individuals aged 40 years and over showed a negative association between serum TSH and eGFR [6]. This study also showed that CKD (eGFR < 60 ml/min/1.73 m^2)

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was more frequent in subjects with subclinical hypothyroidism (odds ratio, OR, 1.63, 95% confidence intervals, CI, 1.38–1.93) and overt hypothyroidism (OR 1.98, 95% CI 1.22–3.20).

From a practical clinical perspective, it is important to obtain robust epidemiological data on the influence of hypothyroidism and hyperthyroidism on renal function. Hence, we used a large community-based cohort of adults aged ≥60 years to assess whether hyperthyroidism and hypothyroidism, as well as thyroid hormone levels (i.e. thyroid stimulating hormone {TSH} and free T4 {FT4}) were independently associated with the prevalence of CKD.

2. Methods

2.1. Study population

The Blue Mountains Eye Study (BMES) is a population-based study of participants aged ≥49 years, living in two postcodes of the Blue Mountains region, west of Sydney, Australia, which has studied age-related eye diseases and other health outcomes in an older urban Australian population. Details of the study methods have previously been described [7]. In brief, during 1992–4, 3654 participants 49 years or older were examined (82.4% participation; BMES-1). Surviving baseline participants were invited to attend 5-year follow-up examinations (1997–9, BMES-2), at which 2334 (75.1% of survivors) and an additional 1174 newly eligible residents were examined, i.e. those who had become eligible by moving into the area or into the age bracket of the original survey. At the 10-year follow-up (2002–4, BMES-3), 1952 participants (75.6% of BMES-1 survivors) were re-examined, respectively. The current study is based on cross-sectional data from the 10-year follow-up or BMES-3. The study was approved by the Human Research Ethics Committee of the University of Sydney and was conducted adhering to the tenets of the Helsinki Declaration. Signed informed consent was obtained from all the participants at each examination.

2.2. Thyroid function tests

Testing was carried out on the same day as blood collection at a central laboratory (Institute of Clinical Pathology and Medical Research, Westmead Hospital), including fasting serum lipids and plasma glucose as previously described [8]. Serum TSH was measured using an Abbott AxSYM autoanalyser with analytical sensitivity of 0.03 mIU/L and assay range of 0–100 mIU/L. Intra-assay coefficients of variation (CV) at different TSH concentrations were as follows: 0.3 mIU/L (7.6%), 5.8 mIU/L (4.4%) and 29 mIU/L (3.7%). Inter-assay CV at corresponding TSH concentrations were 6.9, 5.7, and 6.2%, respectively. The Abbot AxSYM system was used to measure FT4 with an assay range of 0–77.2 pmol/L. Assay CV across the analytical range were 1.5–7.7%. All assays conformed to the respective manufacturer's performance specifications, verified in-house.

Normal TSH levels were defined as 0.1–4.0 mIU/L and normal serum FT4 as 11.5–25.0 pmol/L. Overt hyperthyroidism was defined as serum TSH < 0.1 mIU/L and FT4 > 25.0 pmol/L. Overt hypothyroidism was defined as TSH > 4.0 mIU/L and FT4 < 11.5 pmol/L. Subclinical hyperthyroidism was defined as TSH < 0.1 mIU/L with normal FT4 and subclinical hypothyroidism was defined as TSH > 4.0 mIU/L with normal FT4.

2.3. Assessment of CKD

Serum creatinine was measured within 4 h of a fasting venous blood collection using a Hitachi 747 biochemistry analyzer (Roche, http://www.rochediagnostics.com.au/). Serum creatinine data from 2002 to 2004 (BMES-3) onwards was measured in an Isotope Dilution Mass Spectrometry (IDMS) aligned version of the assay. Estimated GFR (eGFR) was the preferred measure of kidney function in the current study. GFR was indirectly estimated using the 4-variable Modification of Diet in Renal Disease Study (MDRD) equation: GFR (mL/min/1.73 m^2) = 186 × (serum creatinine)$^{-1.154}$ × (Age)$^{-0.203}$ × (0.742 if female) (conventional units) [9]. The main outcome of interest was moderate CKD, defined as eGFR of <60 ml/min/1.73 m^2.

At BMES-2 there was a change in the method/assay used to measure serum creatinine, hence, some creatinine measures were IDMS aligned, while some were not. Moreover, serum TSH and FT4 measures were only obtained from BMES-2 onwards. Given the inconsistencies in the 5-year serum creatinine data we chose not to analyze this in the current report, rather we focused on information collected at BMES-3 (10-year data), specifically, serum creatinine and thyroid function measures.

2.4. Collection of other information

At face-to-face interviews with trained interviewers, a comprehensive medical history that included information about demographic factors, socio-economic characteristics and lifestyle factors like smoking was obtained from all participants. History of smoking was defined as never, past, or current smoking. Current smokers included those who had stopped smoking within the past year. Diabetes was defined either from history or by fasting blood glucose ≥7.0 mmol/L. Subjects were defined as having hypertension if they had systolic blood pressure greater than 140 mm Hg or diastolic blood pressure greater than 90 mm Hg or were taking anti-hypertensive medications [10]. Body mass index (BMI) was calculated as weight divided by height squared (kg/m^2).

2.5. Statistical analysis

SAS statistical software (SAS Institute, Cary, NC) version 9.1 was used for analyses including *t*-tests, χ^2-tests and logistic regression. The association between thyroid dysfunction and CKD was examined in logistic regression models, adjusting first for age and sex, and then further adjusting for confounders that were found to be significantly associated with CKD and/or thyroid dysfunction (i.e. receipt of pension payment, smoking, BMI, diabetes mellitus, and hypertension). Results of logistic regression analyses are expressed as adjusted OR with 95% CI. Statistical significance was defined as $p < 0.05$.

3. Results

Of the 1952 participants at BMES-3, 1571 had complete serum creatinine, TSH, and FT4 measures and hence, were included for analyses. Table 1 shows the study characteristics of participants with and without CKD. Participants with CKD versus those without were more likely to be older, male, receive pension payment, and have higher serum TSH and FT4, and higher prevalence of hypertension and diabetes.

At BMES-3 there were 125 and 1446 participants with and without any level of thyroid dysfunction, respectively. Of the 125 with thyroid disease, 46 self-reported thyroid-related treatment at either one of the examinations (i.e. BMES-1, -2 and/or -3), 43 were currently taking thyroid medication at BMES-3 (40 on thyroxin and 3 on anti-thyroidal medications), 5 self-reported a history of radioactive iodine therapy and 15 had a history of thyroid surgery. After adjusting for age, sex, receipt of pension, BMI, smoking, hypertension and diabetes, participants with any level of thyroid dysfunction compared to those with normal thyroid function had a significantly higher likelihood of having eGFR < 60 ml/min/1.73 m^2, OR 1.67 (95% CI 1.05–2.65). Fig. 1