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Original Article

Glomerular filtration rate is associated with free triiodothyronine in euthyroid subjects: Comparison between various equations to estimate renal function and creatinine clearance

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ABSTRACT

Background: Effects of variations in thyroid function within the euthyroid range on renal function are unclear. Cystatin C-based equations to estimate glomerular filtration rate (GFR) are currently advocated for mortality and renal risk prediction. However, the applicability of cystatin C-based equations is discouraged in patients with overt thyroid dysfunction, since serum cystatin C and creatinine levels are oppositely affected by thyroid dysfunction. Here, we compared relationships of thyroid stimulating hormone (TSH), free thyroxine (FT4) and free triiodothyronine (FT3) with various measures of kidney function in euthyroid subjects.

Methods: Relationships of eGFR, based on creatinine (eGFR*crea*), cystatin C (eGFR*cysC*), creatinine + cystatin C combined (eGFR*crea-cysC*) and creatinine clearance (CrCl) with TSH, FT4 and FT3 were determined in 2180 euthyroid subjects (TSH, FT4 and FT3 all within the reference range; anti-thyroid peroxidase autoantibodies negative) who did not use thyroid hormones, anti-thyroid drugs, amiodarone or lithium carbonate.

Results: In multivariable models including TSH, FT3 and FT4 together, eGFR*crea*, eGFR*cysC* and eGFR*crea-cysC* and CrCl were all positively related to FT3 ($P \leq 0.001$), translating into a 2.61 to 2.83 mL/min/1.73 m^2 increase in eGFR measures and a 3.92 mL/min increase in CrCl per 1 pmol/L increment in FT3. These relationships with FT3 remained taking account of relevant covariates.

Conclusions: In euthyroid subjects renal function is associated with thyroid function status, especially by serum FT3, irrespective of the eGFR equation applied. In the euthyroid state, cystatin C-based eGFR equations are appropriate to assess the relationship of renal function with variation in thyroid function status.

1. Introduction

It is well recognized that thyroid function status has a considerable impact on renal function [1,2]. Thyroid hormones influence many aspects of kidney physiology, including renal hemodynamics, tubular water and electrolyte handling and renin release [1,2]. Overt hypothyroidism reversibly decreases renal blood flow and glomerular filtration rate (GFR), whereas opposite changes are found in hyperthyroidism [1,2,3]. Chronic kidney disease (CKD) is common in the general population [4], and has been found to predict all-cause and cardiovascular mortality [5]. In line with the intricate interaction between thyroid hormone status and renal function, a lower GFR is proportional to an increased prevalence of hypothyroidism [6]. Accordingly, higher thyroid stimulating hormone (TSH), lower free thyroxine (FT4) and lower triiodothyronine (T3) levels confer an increased prevalence of CKD and lower GFR estimates [7,8,9].

Recently, the concept has emerged that low-normal thyroid function, as inferred from a higher thyroid stimulating hormone (TSH) and/or lower circulating FT4 and free T3 (FT3) within the euthyroid range likely has consequences for several health issues, including cardiometabolic disorders and renal function [3,10]. In the Norwegian Hunt study, a higher TSH level within the euthyroid reference range was associated with a lower GFR, as estimated by the serum creatinine-based Modification Diet in Renal Disease (MDRD) formula (11). In a Taiwanese survey, in which the MDRD formula was applied as well, estimated GFR (eGFR) was also associated with a higher TSH within the euthyroid range [12]. Nonetheless, the extent to which GFR in euthyroid individuals is associated with FT3, which is generally considered to be the active thyroid hormone [13], is still largely unknown.

The Chronic Kidney Disease Epidemiology (CKD-EPI) collaboration

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has demonstrated that their novel serum creatinine-based eGFR estimation equation (eGFR*crea*) outperforms GFR estimation based on the MDRD formula (14). In the past few years, cystatin C-based eGFR equations, based on cystatin C alone (eGFR*cysC*) or creatinine + cystatin C combined (eGFR*crea-cysC*) have been developed to estimate GFR [15]. The eGFR*crea-cysC* equation has been shown to provide a better GFR estimate [15]. eGFR*cysC* and eGFR*crea-cys C* are more accurate in predicting death and end-stage renal disease than eGFR based on creatinine alone [16]. Remarkably, serum cystatin C is likely to be differently affected by thyroid dysfunction compared to serum creatinine [17,18,19,20,21]. In fact, serum cystatin C increases in response to levothyroxine treatment in overt hypothyroidism and decreases after restoration of the euthyroid state in hyperthyroidism, contrasting a decrease in serum creatinine after treatment of hypothyroidism [18,20,21]. Likewise, cystatin C is decreased in subclinical hypothyroidism and declines after normalization of subclinical hyperthyroidism [17]. In another report, both subclinical hypothyroidism and subclinical hyperthyroidism resulted in serum cystatin C elevations and hence in lower eGFR*cysC* and in incorrect CKD classification [19]. All together, these findings [17,18,19,20,21] cast considerable doubt as to whether it is appropriate to use cystatin C-based eGFR equations in patients with thyroid dysfunction. In the absence of data regarding the strength of the association of creatinine-based vs. cystatin C-based GFR estimates with variations in thyroid function within the euthyroid range we carried out the present cross-sectional analyses in a well-characterized population-based cohort of euthyroid subjects,

The aim of this study was, therefore, to compare the association of four GFR measures, i.e. GFR*crea*, GFR*cysC*, GFR*crea-cysC* and creatinine clearance (CrCl) with TSH, FT4 and FT3. To this end, we used data from the Prevention of Renal and Vascular End-Stage Disease (PREVEND) study, which has focus on the renal function and albuminuria.

2. Subjects and methods

2.1. Population, measurements and definitions

The protocol of the PREVEND (Prevention of Renal and Vascular End Stage Disease) study has been described in detail elsewhere [22,23,24]. In short, between 1997 and 1998 all inhabitants; aged 28–75 years, of the city of Groningen, the Netherlands (n = 85,421) were asked to send a morning urine sample and to fill out a short questionnaire. Urinary albumin concentration was determined in the samples of the 40,856 responders. Subjects with a urinary albumin concentration > 10 mg/L (n = 7768) were invited to participate of whom 6000 were included. Additionally, 3394 randomly selected subjects with a urinary albumin concentration < 10 mg/L were invited of whom 2592 were enrolled. Together, these 8592 subjects constitute the PREVEND cohort. Pregnant women and diabetic subjects using insulin were excluded. The medical ethics committee of the University Medical Center Groningen, the Netherlands approved the study; which was performed in accordance with Declaration of Helsinki guidelines. All participants gave written informed consent. For the current analysis, we excluded subjects of whom serum creatinine and/or cystatin C measurements were not available and subjects of whom creatinine in two consecutively collected 24 hour urine specimens were missing. TSH, FT4 and FT3 were measured in a randomly selected subset of participants [25]. For the present study we additionally excluded subjects not being euthyroid, using thyroid hormones, antithyroid drugs, amiodarone or lithium carbonate. Euthyroidism was defined as TSH, FT4 and FT3 levels each within the respective reference range as provided by the manufacturer (see Laboratory analyses) [25]. Finally, we also excluded subjects with positive anti-thyroid peroxidase autoantibodies (cut-off value: see Laboratory analyses). Applying these selection criteria 2180 subjects were eligible for the current analyses.

Patient characteristics including age, sex, alcohol use, smoking status, body mass index (BMI), systolic and diastolic blood pressure were obtained. Information on medication use was combined with information from a pharmacy-dispensing registry, which has complete information on > 95% of subjects in the PREVEND cohort. The presence of a self-reported history of myocardial infarction, percutaneous coronary intervention, coronary artery bypass surgery, stroke or the diagnosis of narrowing of one or both carotid arteries was defined as CVD. Hypertension was defined as a systolic blood pressure > 140 mm Hg and/or a diastolic blood pressure > 90 mm Hg and/or the use of blood pressure lowering drugs. Type 2 diabetes mellitus (T2DM) was defined as a fasting serum glucose concentration > 7.0 mmol/L, a non-fasting plasma glucose concentration > 11.1 mmol/L, a self-report of a physician diagnosis, or the use of glucose-lowering drugs. Alcohol consumption was categorized into < 1/≥ 1 drink per day. Smoking was categorized into current, former and never.

The participants were instructed to give venous blood samples after an overnight fast for measurement of creatinine, cystatin C, glucose, total cholesterol, TSH, FT4 and FT3. Urinary albumin excretion (UAE) was documented as the mean of two 24-h urine collections. BMI was defined as weight (kg) by height (m) squared. BP was measured for 10 min at 1-min intervals in the supine position using automatic instrumentation (Dinamap XL Model 9300; Johnson-Johnson Medical, Tampa, FL); reported values were the means of the last two recordings [22,23,26].

eGFR*crea*, eGFR*cysC and* eGFR*crea-cys* were calculated applying Chronic Kidney Disease Epidemiology Collaboration equations (Supplemental Table 1) [14,15]. CrCL (in mL/min) was determined using two 24-hour urine samples with the formula: CrCl = urinary creatinine concentration (mmol/L) ∗ 24-hour urinary volume (mL)/(serum creatinine (μmol/L) ∗ 1.44). The results of two measurements were averaged for analysis.

2.2. Laboratory analyses

Heparinized plasma samples and sera were stored at − 80 °C until analyses. Serum TSH (Architect; Abbott Laboratories, Abbott Park, IL, USA; reference range 0.35–4.94 mU/L), FT4 (AxSYM; Abbott Laboratories, Abbott Park, IL, USA; reference range 9.14–23.81 pmol/L) and FT3 (AxSYM; Abbott Laboratories, Abbott Park, IL, USA; reference range; 2.23–5.35 pmol/L) were measured by microparticle enzyme immunoassays. Anti-thyroid peroxidase autoantibodies were determined using commercially available automated enzyme linked immunoassays (Abbott Laboratories, Abbott Park, IL, USA; kit number 5F57). Anti-thyroid peroxidase autoantibodies were considered positive using a cut-off value as indicated by the supplier (≥ 12 kU/L).

Total serum cholesterol and plasma glucose were measured using Kodak Ektachem dry chemistry (Eastman Kodak, Rochester, NY, USA). Serum creatinine was measured by an enzymatic method on a RocheModular analyzer (Roche Diagnostics, Mannheim, Germany). Serum cystatin C was measured by Gentian Cystatin C Immunoassay (Gentian AS, Moss, Norway) on a Modular analyzer (Roche Diagnostics). Urinary albumin concentration was measured by nephelometry with a threshold of 2.3 mg/L (Dade Behring Diagnostic, Marburg, Germany).

2.3. Statistical analyses

Data analysis was performed using IBM SPSS software (version 23.0, SPSS Inc. Chicago, IL, USA). Normally distributed data are given as mean ± SD and non-parametrically distributed data are presented as median (interquartile range). Categorical variables are given as percentages. TSH values and UAE were natural logarithm ($\log_e$) transformed to achieve approximately normal distributions. Comparisons of thyroid function parameters between eGFR categories were done by analysis of variance with Bonferroni method to correct for multiple comparisons. Univariate relationships were assessed by Pearson correlation coefficients. Multivariable linear regression analyses were used to determine the relationships of TSH, FT4 and FT3 together on renal