ORIGINAL ARTICLE

Thyroid function, renal events and mortality in chronic kidney disease patients: the German Chronic Kidney Disease study

Ulla T. Schultheiss[1,2], Inga Steinbrenner[1], Matthias Nauck[3], Markus P. Schneider[4], Fruzsina Kotsis[1,2], Seema Baid-Agrawal[5], Elke Schaeffner[6], Kai-Uwe Eckardt[4,7], Anna Köttgen[1] and Peggy Sekula[1]; the GCKD investigators

[1]Institute of Genetic Epidemiology, Medical Center – University of Freiburg, Faculty of Medicine, Freiburg, Germany, [2]Department of Medicine IV – Nephrology and Primary Care, Medical Center - University of Freiburg, Faculty of Medicine, Freiburg, Germany, [3]Institute of Clinical Chemistry and Laboratory Medicine, University Medicine Greifswald, Greifswald, Germany, [4]Department of Nephrology and Hypertension, University Hospital Erlangen, Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany, [5]Department of Nephrology and Transplant Center, Sahlgrenska University Hospital, University of Gothenburg, Gothenburg, Sweden, [6]Institute of Public Health, Charité–Universitätsmedizin Berlin, Berlin, Germany and [7]Department of Nephrology and Medical Intensive Care, Charité–Universitätsmedizin Berlin, Berlin, Germany

Correspondence to: Ulla T. Schultheiss; E-mail: ulla.schultheiss@uniklinik-freiburg.de

ABSTRACT

Background. Hypothyroidism and low free triiodothyronine (FT3) syndrome [low FT3 levels with normal thyroid-stimulating hormone (TSH)] have been associated with reduced kidney function cross-sectionally in chronic kidney disease (CKD) patients with severely reduced estimated glomerular filtration rate (eGFR) or end-stage kidney disease (ESKD). Results on the prospective effects of impaired thyroid function on renal events and mortality for patients with severely reduced eGFR or from population-based cohorts are conflicting. Here we evaluated the association between thyroid and kidney function with eGFR (cross-sectionally) as well as renal events and mortality (prospectively) in a large, prospective cohort of CKD patients with mild to moderately reduced kidney function.

Methods. Thyroid markers were measured among CKD patients from the German Chronic Kidney Disease study. Incident renal endpoints (combined ESKD, acute kidney injury and renal death) and all-cause mortality were abstracted from hospital records and death certificates. Time to first event analysis of complete data from baseline to the 4-year follow-up (median follow-up time 4.04 years) of 4600 patients was conducted. Multivariable linear regression and Cox proportional hazards models were fitted for single and combined continuous thyroid markers [TSH, free thyroxine (FT4), FT3] and thyroid status.

Results. Cross-sectionally, the presence of low-FT3 syndrome showed a significant inverse association with eGFR and continuous FT3 levels alone showed a significant positive association with eGFR; in combination with FT4 and TSH, FT3 levels also showed a positive association and FT4 levels showed a negative association with eGFR. Prospectively, higher FT4 and lower FT3 levels were significantly associated with a higher risk of all-cause mortality ($N_{events} = 297$). Per picomole per litre higher FT3 levels the risk of reaching the composite renal endpoint was 0.73-fold lower (95% confidence interval 0.65–0.82; $N_{events} = 615$). Compared with euthyroid patients, patients with low-FT3 syndrome had a 2.2-fold higher risk and patients with hypothyroidism had a 1.6-fold higher risk of experiencing the composite renal endpoint.

Conclusions. Patients with mild to moderate CKD suffering from thyroid function abnormalities are at an increased risk of adverse renal events and all-cause mortality over time.

Keywords: chronic kidney disease, mortality, renal events, thyroid function, thyroid status

INTRODUCTION

Chronic kidney disease (CKD) is recognized as a global health problem due to its high cost, reduced patient quality of life [1], high comorbidities and poorer prognosis of other diseases such as metabolic diseases [2]. The thyroid gland influences metabolic processes in the body and clinical/translational research supports a connection between thyroid and kidney function. Patients with CKD and end-stage kidney disease (ESKD) are prone to hypothyroidism [3–9] and low free triiodothyronine (FT3) syndrome [combined low FT3 levels with normal thyroid-stimulating hormone (TSH) levels] [6, 10]. Thyroid function can also affect kidney function, CKD progression, and increase cardiovascular disease (CVD) disease risk. CKD patients have a high risk for CVD and impaired thyroid function may increase their CVD risk as well as mortality, as has been shown for ESKD patients [11, 12]. Zoccali *et al.* [13] reported T3 to be a strong marker of survival in ureamic patients. Fan *et al.* [14] reported a high prevalence of low-T3 syndrome in a very small cohort of CKD patients with severely reduced kidney function and patients with ESKD, suggesting low-T3 syndrome to be a risk factor of CKD progression. Rhee *et al.* [11] reported hypothyroidism to be associated with higher mortality in haemodialysis patients. Despite the strong evidence supporting a connection of thyroid and kidney function, the directionality and causality of the association are still unclear [15] and little is known about the influence of impaired thyroid function on patients with moderately reduced estimated glomerular filtration rate (eGFR), making the implementation of preventive measures for this high-risk subpopulation difficult.

We therefore set out to evaluate the cross-sectional and prospective association of thyroid function markers (TFMs) and the presence of thyroid dysfunction, defined as hypothyroidism, hyperthyroidism and low-FT3 syndrome, with eGFR (cross-sectionally), all-cause mortality (prospectively) and a composite renal endpoint [ESKD, acute kidney injury (AKI), death due to untreated ESKD; prospectively] in a large German cohort of mostly CKD Stage 3 patients, the German Chronic Kidney Disease (GCKD) study.

MATERIALS AND METHODS

Study population

The GCKD study is a prospective European ancestry cohort study of 5217 CKD patients, ages 18–76 years at baseline (2010–12), under regular nephrologist care [16, 17]. The major inclusion criteria were reduced eGFR of 30–60 mL/min/1.73 m^2 or proteinuria, defined as a urinary albumin:creatinine ratio (UACR) >300 mg/g with an eGFR >60 mL/min/1.73 m^2. Patients undergo regular, standardized study visits, questionnaire-based interviews, physical examinations and bio-sampling by trained personnel. All hospital discharge records, death certificates and records from treating nephrologists are collected continuously. The GCKD study was approved by all the ethics committees of the participating institutions and registered in the national registry for clinical studies (DRKS 00003971). Written informed consent was obtained from all participants.

Baseline variables

Serum and urinary creatinine was determined using an isotope dilution mass spectrometry (IDMS)-traceable methodology (Creatinine plus, Roche, Basel, Switzerland). Urinary albumin was determined using a turbidimetric method (Tina-quant, Roche). GFR (mL/min/1.73 m^2) was estimated using the creatinine-based Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [18]. Serum cholesterol was measured using an enzymatic test for direct quantitative identification of cholesterol [CHOD-PAP; Modular (P), Roche].

TFM was measured in 2014–15 from baseline specimens stored at $-80°C$ at the Institute of Clinical Chemistry and Laboratory Medicine, Greifswald, Germany, TSH was determined using a chemiluminescence approach (Dimension VISTA, Siemens Healthcare Diagnostics, Deerfield, IL, USA) and free thyroxine (FT4) and FT3 were determined using a competitive immunoassay method (Dimension VISTA, Siemens Healthcare Diagnostics). Interassay coefficients of variation are listed in Supplementary data, Table S1. Thyroid functional status (euthyroidism, hypothyroidism, hyperthyroidism or low-FT3 syndrome) was based on reference ranges [19–21] of TSH (0.49–3.29 mU/L), FT4 (9.8–18.8 pmol/L) and FT3 (3.3–6.1 pmol/L) levels:

- euthyroidism: TSH, FT3, FT4 within reference ranges;
- hypothyroidism (subclinical and overt): TSH >3.29 mU/L and FT4 within the reference range or <9.8 pmol/L;
- hyperthyroidism (subclinical and overt): TSH <0.49 mU/L and FT4 and FT3 within or above the reference range and
- low-FT3 syndrome: FT3 <3.3 pmol/L and TSH within the reference range.

Uncategorized patients with TFM distributions not covered by any of the above categories were considered as 'undefined' ($n = 196$).

Medication intake was obtained using the Anatomical Therapeutic Chemical (ATC) classification system. Patients were evaluated for the intake of thyroid medication (ATC codes:

thyroid hormones, H03A; antithyroid medication, H03B) and anti-arrhythmic medication (ATC code: C01B).

Diabetes mellitus (DM) was defined as haemoglobin A1c ≥6.5% or intake of anti-diabetic medication. Amputation corrected body mass index (BMI) was calculated from weight and height. Age, sex, centre and smoking were based on self-reports at enrolment. A positive history of CVD was determined by a positive medical history for stroke (defined as either stroke or carotid artery operation/stenting), peripheral arterial disease (defined as either amputation or peripheral artery operation/stenting) and/or coronary heart disease (defined as either myocardial infarction or bypass operation or percutaneous coronary intervention).

Prospective endpoint abstraction

Endpoints are continuously abstracted from hospital discharge letters, nephrologist outpatient letters and death certificates based on a standardized, specific endpoint abstraction catalogue. To guarantee quality and reduce interobserver variability, endpoints were abstracted by a specialized endpoint committee consisting of four medical doctors. Difficult cases were discussed within the team. Quality control was ensured by conducting regular ring trials. Abstracted event data from the first 4 years of follow-up were available (median 4.04 years). Events of interest were all-cause mortality (defined as any death; $N_{death\ events} = 297$) and a composite renal endpoint consisting of ESKD, AKI or renal death ($N_{events} = 615$: $N_{ESKD\ events} = 155$, $N_{AKI\ events} = 456$, $N_{renal\ death\ events} = 4$). ESKD was defined as either the start of any form of dialysis or kidney transplantation. AKI was defined by applying the Acute Kidney Injury Network (AKIN) criteria [22] using available creatinine values for each patient. Creatinine values of the acute event were compared with the last creatinine values recorded from each patient before the event. Lastly, AKI events were also abstracted for patients requiring temporary dialysis. In order to ensure homogeneity, only AKIs requiring hospital admission were abstracted.

Statistical analyses

Cross-sectional baseline characteristics of patients by thyroid status were compared using chi-squared and Kruskal–Wallis tests for variables as appropriate (Table 1).

For statistical analyses, patients on anti-arrhythmic medication as well as one further patient with highly incomplete data at baseline and follow-up were excluded from the GCKD cohort ($N = 5102$; Supplementary data, Figure S1). For the main analyses, patients with any missing information on relevant variables were additionally excluded from the GCKD cohort (analysis set $n = 4600$; Supplementary data, Table S2). TSH and UACR were logarithmically transformed before analyses due to skewed distributions.

Cross-sectional analysis. To evaluate the association of each thyroid trait [log(TSH), FT4 and FT3] and thyroid functional status with eGFR (outcome), different linear regression models were fitted: unadjusted (Model 1), minimally adjusted (age, sex and centre; Model 2) and fully adjusted [age, sex, centre, BMI, history of CVD, DM, cholesterol and log(UACR); Model 3]. In addition, the same models were fitted that simultaneously contained all three thyroid traits (Supplementary data, Table S3).

Table 1. Baseline characteristic of the analysis set (N = 4600) and by thyroid functional status

Variable	Analysis set (N = 4600)	Euthyroidism (n = 3404)	Hypothyroidism (n = 221)	Hyperthyroidism (n = 539)	Low-FT3 syndrome (n = 240)	Undefined[c] (n = 196)	P-value*
Age (years)	60.0 ± 12.1	59.5 ± 12.2	55.7 ± 14.9	62.7 ± 9.5	63.2 ± 10.8	60.7 ± 11.4	<0.001
Men	2733 (59.4)	2146 (63.0)	115 (52.0)	277 (51.4)	96 (40.0)	99 (50.5)	<0.001
eGFR[a] (mL/min/1.73 m^2)	49.6 ± 18.4	50.3 ± 18.2	51.0 ± 23.0	47.5 ± 16.7	43.5 ± 16.8	48.7 ± 19.5	<0.001
UACR[b] (mg/g), mean (IQR)	52.5 (9.7–393.7)	55.4 (10.0–395.1)	190.1 (14.2–949.3)	27.3 (7.1–231.1)	51.1 (11.1–376.0)	46.8 (8.4–333.3)	<0.001
TSH[a,b] (mU/L), mean (IQR)	1.2 (0.8–1.8)	1.3 (0.9–1.8)	4.1 (3.7–4.9)	0.3 (0.1–0.4)	1.3 (0.9–1.6)	0.9 (0.5–1.6)	<0.001
FT4[a] (pmol/L)	14.3 ± 2.9	13.9 ± 1.8	13.5 ± 2.2	16.4 ± 3.6	15.0 ± 3.2	15.7 ± 8.2	<0.001
FT3[a] (pmol/L)	4.2 ± 0.7	4.3 ± 0.5	4.1 ± 0.8	4.4 ± 0.9	3.0 ± 0.4	4.0 ± 1.3	<0.001
Thyroid medication intake[d], n (%)	1043 (22.7)	512 (15.0)	73 (33.0)	264 (49.0)	109 (45.4)	85 (43.4)	<0.001
Thyroid hormone intake, n (%)	965 (21.0)	453 (13.3)	68 (30.8)	253 (46.9)	108 (45.0)	83 (42.4)	<0.001
Anti-thyroid medication, n (%)	78 (1.7)	59 (1.7)	5 (2.2)	11 (2.1)	1 (0.4)	2 (1.0)	0.168
Current smoking,[a] n (%)	731 (15.9)	558 (16.4)	30 (13.6)	75 (13.9)	43 (17.9)	25 (12.8)	0.264
DM, n (%)	1628 (35.4)	1164 (34.2)	69 (31.2)	197 (36.6)	111 (46.3)	87 (44.4)	<0.001
BMI[a] (kg/m^2)	29.7 ± 6.0	29.6 ± 5.8	30.2 ± 6.4	29.3 ± 5.4	30.2 ± 7.1	31.3 ± 7.2	0.017
History of CVD,[a] n (%)	1369 (29.8)	995 (29.2)	60 (27.2)	156 (28.9)	90 (37.5)	68 (34.7)	0.033
Hypertension,[a] n (%)	4424 (96.2)	3274 (96.2)	212 (95.9)	523 (97.0)	227 (94.6)	188 (95.9)	0.592
Cholesterol[a] (mg/dL)	211.6 ± 53.0	210.6 ± 48.7	234.1 ± 80.1	208.9 ± 50.4	210.3 ± 71.2	211.2 ± 61.3	<0.001
HDL cholesterol[a,b] (mg/dL), mean (IQR)	48.4 (39.4–61.4)	48.2 (39.2–60.8)	50.1 (40.3–61.2)	49.6 (39.6–63.1)	49.8 (40.4–66.4)	48.0 (39.6–60.4)	0.228

Values are presented as mean ± standard deviation unless stated otherwise. eGFR, UACR, TSH: mU/L; FT4: pmol/L; FT3: pmol/L; low-FT3 syndrome: low FT3 levels in combination with normal TSH levels; IQR: interquartile range; HDL: high-density lipoprotein.
[a]Missing covariate information in the GCKD cohort: TSH (n = 339), FT4 (n = 5), FT3 (n = 4), eGFR (n = 27), smoking (n = 13), cholesterol (n = 7), HDL (n = 5), BMI (n = 49), UACR (n = 64) and hypertension (n = 2).
[b]Skewed distribution: variables displayed as p50 (p25–p75).
[c]Undefined refers to patients that could not be assigned to one of the four thyroid functional categories by their respective thyroid hormone levels.
[d]Thyroid hormone intake plus anti-thyroid medication.
*Reported P-values for difference: χ^2 (categorical) and Kruskal–Wallis tests (continuous) for variables as appropriate.

Analysis of prospective endpoints. For the association analysis of thyroid traits and thyroid functional status with prospective endpoints (all-cause mortality and composite renal endpoint), Cox proportional hazards regression analysis was conducted to evaluate the time from study entry to first respective event, whichever occurred first [23] (Supplementary data, Tables S4 and S5). Multiple/recurrent events in a patient were thereby ignored. Models similar to the cross-sectional analysis were fitted for TFM (single and combined) as well as for thyroid functional status: unadjusted (Model 1), minimally adjusted (Model 2) and fully adjusted (Model 3). Estimated risks are expressed as hazard ratios (HRs) for all-cause mortality and cause-specific HRs for the composite renal endpoint, with death from other causes as the competing event [24].

Competing events analysis used the same models. Subdistribution hazard analyses were carried out for the composite renal endpoint evaluating potential indirect effects of markers on the composite renal endpoint [25] (Supplementary data, Table S6). Cumulative incidence functions were plotted. Proportional hazards assumptions were checked with Schoenfeld's residuals, with no major deviations (data not shown).

Statistical significance. A Bonferroni correction that accounts for the three thyroid markers and two outcomes was applied to define statistical significance: P-values $<0.05/(3 \times 2) = 8.3 \times 10^{-3}$ were considered significant. Spearman correlation between all markers ranged from -0.203 to 0.072.

Adjustment variables. Prior to the reported analysis, adjustment variables were selected via a two-step procedure: literature-based biological plausibility followed by variable selection using backward elimination based on the Akaike information criterion in regression models that did not contain thyroid markers (Supplementary data, Table S7). Ultimately, one common adjustment variable set was chosen to be used in Model 3 (fully adjusted).

Additional analyses. In order to validate results obtained from the main analysis based on complete cases, two additional analyses were carried out:

i. Imputed data analysis: The generation of the dataset used in the main analysis led to the additional exclusion of 502 patients due to incomplete data (10%; Supplementary data, Figure S1). We used a multiple imputation approach (R package 'mice', R foundation, Vienna, Austria) to generate 10 complete datasets for each outcome by repeatedly replacing missing values using chained equations (default setting) [26]. The imputation was done on the GCKD cohort excluding the one patient with highly incomplete data at baseline and follow-up ($n = 5216$). Per outcome, the same analyses as in the main analysis (excluding patients on anti-arrhythmic drugs) were then conducted in each complete imputed dataset ($n = 5102$). Afterwards, single estimates were pooled to obtain combined estimates for all associations reported from the main analysis [26] (Supplementary data, Tables S8–S10).

ii. Sensitivity analysis: Since almost one-quarter of all patients were under thyroid hormone substitution (21.0%), another dataset that only included patients not treated for thyroid disorders was defined ($n = 3557$; Supplementary data, Figure S1) in order to investigate whether treatment of patients changes the association of thyroid function with eGFR, the

composite renal endpoint and mortality (Supplementary data, Tables S11–S14). The same analyses as in the main analysis were carried out to contrast the results of the main analysis.

RESULTS

Table 1 gives an overview of patient characteristics by thyroid functional status for the analysis set. Compared with euthyroid patients (59.5 years), hypothyroid patients tended to be younger (55.7 years), have higher UACR values and a lower percentage are men. Patients with hyperthyroidism (62.7 years) were older than euthyroid patients. Other differences between the euthyroid patient group and thyroid disease groups included older age, lower eGFR and higher comorbidity rates for diabetes and a history of CVD in the low-FT3 syndrome group. A P-value for difference using the chi-squared test for categorical and Kruskal–Wallis test for continuous variables showed significant results for age, sex, eGFR, UACR, diabetes and cholesterol.

Supplementary data, Table S2 compares the GCKD cohort ($N = 5217$) with the analysis set ($n = 4600$; exclusion of patients with missing variable information [$n = 502$]) and the sensitivity set ($n = 3557$; restriction to patients not treated for thyroid disorders). The analysis set was similar to the GCKD cohort except for slightly higher median UACR values in the analysis cohort (50.9 versus 52.5 mg/g).

Differences between the analysis set and the sensitivity set were a higher proportion of men (59.4 versus 66.3%) and a higher median UACR (52.5 versus 64.4 mg/g) in the sensitivity set.

Cross-sectional association of TFMs and thyroid functional status with eGFR

Table 2 shows the cross-sectional associations of various thyroid traits on eGFR (mL/min/1.73 m^2).

For TFMs added singularly to the regression model, FT3 (pmol/L) showed a highly significant positive association with eGFR (per 1 pmol/L increase of FT3, eGFR was 2.99 mL/min/1.73 m^2 higher; P = 1.6e–15). For the combined TFM analysis, FT3 showed a highly significant positive association with eGFR (per 1 pmol/L increase of FT3 eGFR was 3.12 mL/min/1.73 m^2 higher; P = 1.6e–16) and FT4 showed a significant negative association with eGFR (per 1 pmol/L increase of FT4 eGFR was 0.27 mL/min/1.73 m^2 lower; P = 2.5e–03). Patients with low FT3 syndrome had a significantly lower eGFR (mL/min/1.73 m^2) than euthyroid patients (effect size -4.68 mL/min/1.73 m^2; P = 3.3e–05).

For analyses in the imputed dataset, results were very similar (Supplementary data, Table S7) to the analysis dataset, but the association with FT4 added singularly to the regression model resulted in a significant negative association with eGFR (per 1 pmol/L increase of FT4 eGFR was 0.22 mL/min/1.73 m^2 lower; P = 7.7e–03).

In the sensitivity analyses excluding patients treated for thyroid disorders, all associations were similar in direction and mostly stronger in magnitude (Supplementary data, Table S10) compared with the main analysis, except for smaller effect sizes for TSH in the combined TFM analysis, as well as for hyperthyroid patients and patients from the undefined group compared with euthyroidism.

Table 2. Cross-sectional associations of TFMs and thyroid functional status with eGFR in the analysis set ($n = 4600$)

Model	Effect on eGFR, mL/min/1.73 m^2 (95% CI)	Standard error	P-value
Single TFM[a]			
TSH, log-transformed	−0.15 (−0.67–0.37)	0.26	5.8e–01
FT4	−0.17 (−0.34–0.00)	0.09	5.4e–02
FT3	2.99 (2.26–3.72)	0.37	**1.6e–15**
Combined TFM[b]			
TSH, log-transformed	−0.14 (−0.66–0.39)	0.27	6.1e–01
FT4	−0.27 (−0.45 to −0.10)	0.09	**2.5e–03**
FT3	3.12 (2.38–3.86)	0.38	**1.6e–16**
Euthyroidism versus	Ref	Ref	Ref
Hypothyroidism	−1.62 (−3.92–0.67)	1.17	1.7e–01
Hyperthyroidism	−1.26 (−2.79–0.26)	0.78	1.1e–01
Low FT3 syndrome	−4.68 (−6.89 to −2.47)	1.13	**3.3e–05**
Undefined	−0.90 (−3.32–1.51)	1.23	4.6e–01

TSH, mU/L; FT4, pmol/L; FT3, pmol/L.
Per thyroid trait, linear regression models were fitted and adjusted for age, sex, centre, BMI, history of CVD, DM, UACR (log-transformed), smoking and cholesterol. Significant P-values (P ≤ 8.3e–03) are indicated in bold.
[a]Single TFM: TFMs are added to the regression model singularly.
[b]Combined TFM: all TFMs are entered together into the regression model.

Table 3. Associations of TFMs and thyroid functional status with all-cause mortality in the analysis set (N = 4600, N$_{events}$ = 297)

Model	HR (95% CI)	P-value
Single TFM[a]		
TSH, log-transformed	1.12 (0.97–1.29)	1.1e–01
FT4	1.05 (1.02–1.08)	**4.7e–04**
FT3	0.74 (0.62–0.89)	**1.6e–03**
Combined TFM[b]		
TSH, log-transformed	1.14 (0.99–1.31)	7.2e–02
FT4	1.06 (1.03–1.08)	**8.2e–05**
FT3	0.74 (0.61–0.90)	**2.0e–03**
Euthyroidism versus	Ref	Ref
Hypothyroidism	1.48 (0.90–2.44)	1.2e–01
Hyperthyroidism	1.42 (1.02–1.97)	3.8e–02
Low FT3 syndrome	1.31 (0.84–2.04)	2.3e–01
Undefined	1.53 (0.93–2.53)	9.4e–02

TSH, mU/L; FT4, pmol/L; FT3, pmol/L.
Per thyroid trait, Cox proportional hazards models were fitted and adjusted for the baseline variables: age, sex, centre, eGFR, BMI, history of CVD, DM, UACR (log-transformed), smoking, cholesterol. Significant P-values (P ≤ 8.3e–03) are in bold.
[a]Single TFM: TFMs are added to the regression model singularly.
[b]Combined TFM: all TFMs are entered together into the regression model.

Association of TFMs and thyroid functional status with all-cause mortality

For the single TFM analysis, higher FT3 (per pmol/L) levels were associated with a 0.74-fold lower risk of all-cause mortality [95% confidence interval (CI) 0.62–0.89; N$_{events}$ = 297; Table 3], therefore patients with lower FT3 levels had a higher risk of all-cause mortality.

Moreover, higher FT4 (pmol/L) was significantly associated with a higher hazard for all-cause mortality [hazard ratio (HR) 1.05; P = 4.7e–04]. For the combined TFM analysis, all associations were similar in direction and magnitude (FT3: HR 0.74, P = 2.0e–03; FT4: HR 1.06, P = 8.2e–05).

Neither TSH nor any thyroid diseases were significantly associated with all-cause mortality.

For analyses in the imputed dataset (Supplementary data, Table S8), results were similar in direction and magnitude to the analysis dataset.

In sensitivity analyses, the significance of the association for FT3 (single TFM: HR 0.69, P = 5.3e–04; combined TFM: HR 0.65, P = 7.8e–05) remained (Supplementary data, Table S11) and FT4 only stayed significant for the combined TFM analysis (HR 1.09, P = 1.4e–03).

Association of TFMs and thyroid functional status with the composite renal endpoint

For the single and combined TFM analyses, higher FT3 (per pmol/L) significantly decreased the hazard for a renal event 0.73-fold (Table 4); conversely, lower FT3 (per pmol/L) significantly increased the hazard for a renal event 1.3-fold. To illustrate a potential dose–response relationship, a model including FT3 categorized into quartiles was fitted. Patients in the lowest quartile (0.77–3.81 pmol/L) had a higher hazard for a renal event compared with patients in other quartiles (Figure 1).

Compared with euthyroid patients, the hazard for developing a renal event in patients with low-FT3 syndrome was 2.2-fold higher (Table 4). The hazard for a renal event for hypothyroid patients was also increased 1.6-fold compared with euthyroid patients (Figure 2 and Table 4).

For the imputed dataset, results were similar in direction and magnitude to the analysis dataset (Supplementary data, Table S9).

In the sensitivity analysis (Supplementary data, Table S12), the magnitude and strength of the associations for FT3 (HR 0.76, P = 2.8e–04) and low-FT3 syndrome (HR 1.9, P = 7.5e–04) remained.

The analysis of the competing event and the subdistribution hazard analysis of the composite renal endpoint for the analysis and sensitivity set did not reveal any additional insight (Supplementary data, Tables S6 and S13). Cause-specific HRs and subdistribution HRs were of the same magnitude and level of significance, indicating no indirect effects on the outcome.

DISCUSSION

To the best of our knowledge, the GCKD study is the largest cohort of patients with moderately reduced kidney function; available TSH, FT4 and FT3 measurements; a solely European ethnic background and under regular nephrologist care. This unique setting enables us to follow a large cohort of CKD patients for a long period of time before reaching ESKD, resulting in higher numbers of adverse events and more stable associations. It also clearly separates the GCKD study from advanced CKD/ESKD cohort studies, small-sample CKD cohort studies, population-based cohorts with small numbers of CKD patients and any cross-sectional cohort studies. Since all GCKD patients are under state-of-the-art nephrologist care, the known influence of different levels of care on CKD and ESKD patient outcomes is thus minimized [27, 28].

In our study, we detected a high prevalence of thyroid dysfunction, with about one-quarter of patients classified as hypothyroid either by laboratory tests or thyroid hormone substitution, but also a large proportion of hyperthyroid patients (~10%). Cross-sectionally, we demonstrated that higher FT3 levels alone and lower FT4 in combination with higher FT3 levels were significantly associated with higher baseline eGFR, as well as that low-FT3 syndrome was associated with reduced eGFR compared with euthyroidism. Prospectively, higher FT3 levels alone decreased hazards for all-cause mortality and the composite renal endpoint. In contrast, higher FT4 levels were significantly associated with an increased hazard for all-cause mortality. Moreover, we observed a significant association of hypothyroidism and low-FT3 syndrome compared with euthyroidism with the composite renal endpoint.

The prevalence of hypothyroidism in CKD cohorts is reported to be higher than the prevalence of hypothyroidism in population-based studies and indeed our findings in the GCKD study are higher (~25%) than those from the German population-based Study of Health in Pomerania (SHIP) (4.2%) and Cooperative Health Research in the Augsburg Region (KORA; ~11.8%) studies [20], but comparable to other studies of CKD Stages 3–5 patients, such as the Veterans Health Study [29] (~25% hypothyroidism; different age, sex and ethnic composition). The prevalence of hyperthyroidism has been reported to be the same for CKD patients as for the general population [30]. Our results were analogous to other population-based studies. After restricting the GCKD dataset to participants not treated for thyroid disorders, the prevalence of hyperthyroidism was

Table 4. Associations of TFMs and thyroid functional status with the composite renal endpoint in the analysis set (N = 4600, N_events = 615)

Model	HR (95% CI)	P-value
Single TFM[a]		
TSH, log transformed	1.06 (0.96–1.16)	2.4e–01
FT4	1.01 (0.98–1.04)	7.4e–01
FT3	0.73 (0.65–0.82)	**3.5e–07**
Combined TFM[b]		
TSH, log-transformed	1.06 (0.96–1.16)	2.6e–01
FT4	1.02 (0.99–1.04)	3.1e–01
FT3	0.73 (0.64–0.82)	**3.1e–07**
Euthyroidism versus	Ref	Ref
Hypothyroidism	1.59 (1.16–2.18)	**3.4e–03**
Hyperthyroidism	1.11 (0.85–1.44)	4.4e–01
Low-FT3 syndrome	2.15 (1.65–2.81)	**1.7e–08**
Undefined	1.48 (1.04–2.11)	2.8e–02

TSH, mU/L; FT4, pmol/L; FT3, pmol/L.
Per thyroid trait, Cox proportional hazards models were fitted and adjusted for the baseline variables: age, sex, centre, eGFR, BMI, history of CVD, DM, UACR, smoking, cholesterol. Significant P-values (P ≤ 8.3e–03) are in bold.
[a]Single TFM: TFMs are added to the regression model singularly.
[b]Combined TFM: all TFMs are entered together into the regression model.

Number at risk					
1st quartile	1160	1101	1042	968	581
2nd quartile	1161	1131	1086	1040	654
3rd quartile	1145	1119	1077	1037	624
4th quartile	1134	1110	1085	1050	657
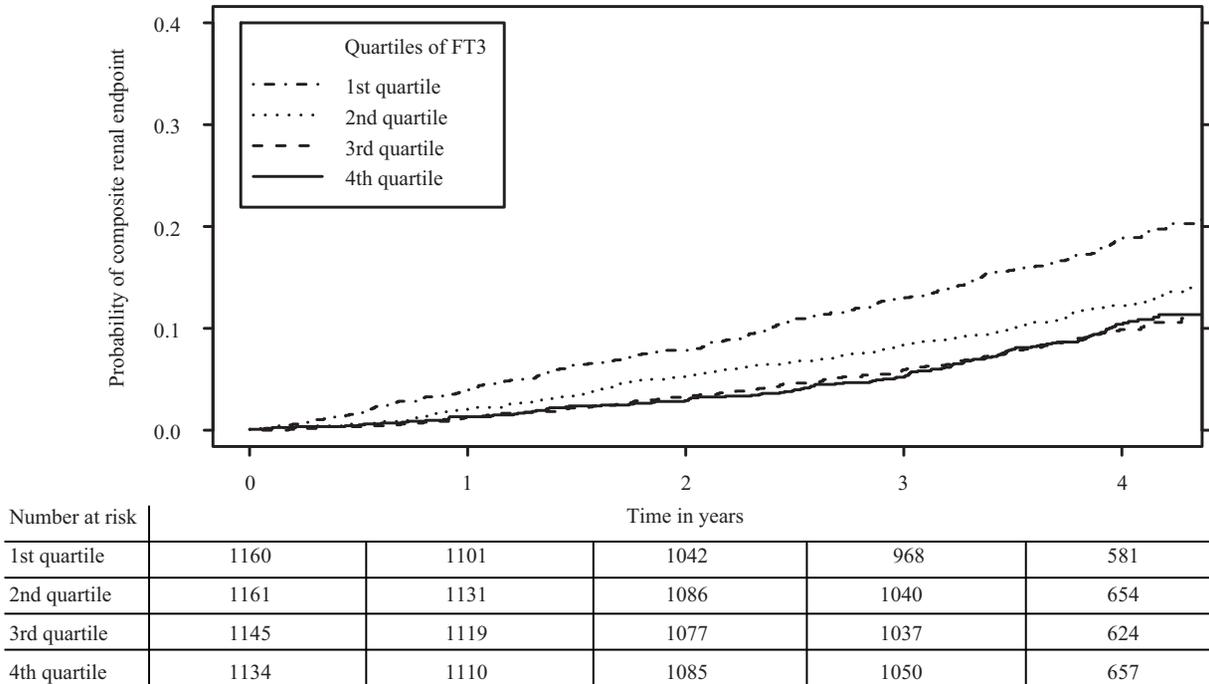
FIGURE 1: Cumulative incidence function for the composite renal endpoint by quartiles of FT3 (*n* = 4600, N_events = 615) in the analysis set. The number of patients at risk per quartile over time is displayed in the adjacent table. FT3 quartile distribution: first quartile: 0.77–3.81 pmol/L; second quartile: 3.82–4.19 pmol/L; third quartile: 4.20–4.57 pmol/L; fourth quartile: 4.58–15.5 pmol/L.
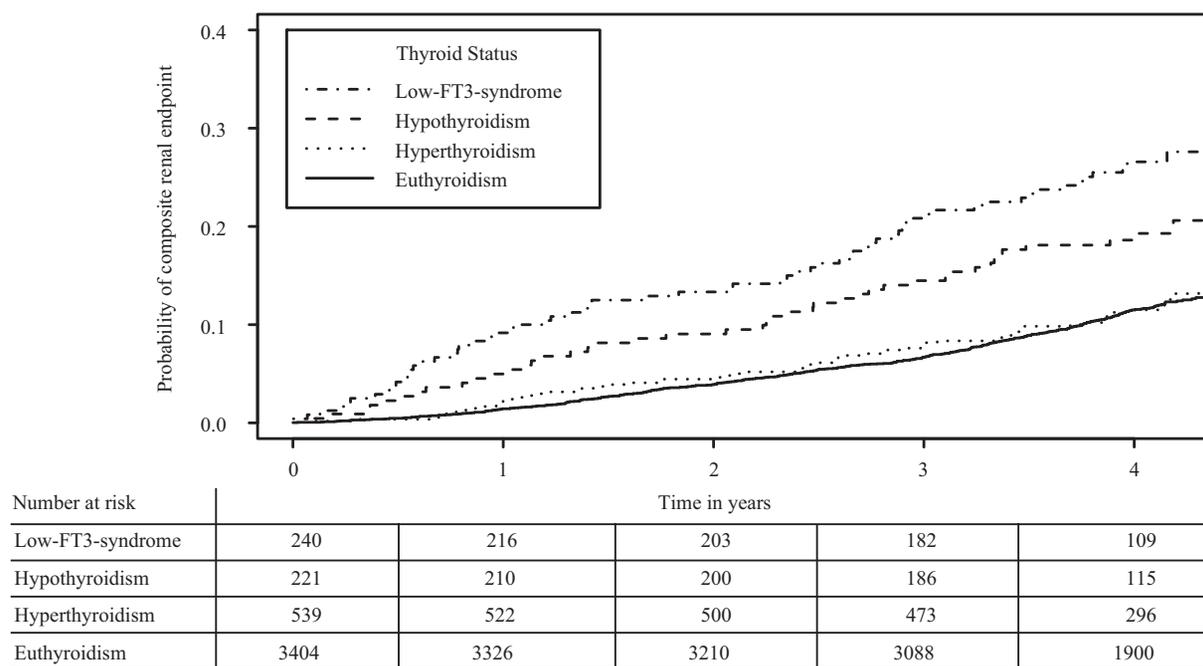
FIGURE 2: Cumulative incidence function for the composite renal endpoint by thyroid functional status ($N = 4600$, $N_{events} = 600$) in the analysis set. The number of patients at risk per thyroid status over time is displayed in the adjacent table. Composite renal endpoint: combined ESKD, AKI and renal death.

Number at risk	Time in years				
Low-FT3-syndrome	240	216	203	182	109
Hypothyroidism	221	210	200	186	115
Hyperthyroidism	539	522	500	473	296
Euthyroidism	3404	3326	3210	3088	1900

similar to that of the German population-based SHIP study [31, 32]. Since 21% of all GCKD patients were on thyroid hormone substitution, we evaluated thyroid functional status for these patients. It should be noted that for patients on thyroid hormone substitution ($n = 925$), 26.1% had prevalent, iatrogenic hyperthyroidism by thyroid hormone constellation. Although we could not detect a higher risk of reaching the composite renal endpoint or death for hyperthyroid patients in our study, hyperthyroidism was previously related to increases in heart rate, cardiac contractility, systolic and mean pulmonary artery pressure, cardiac output, diastolic relaxation and myocardial oxygen consumption [33]. A pathophysiological reason for this increased number of hyperthyroid patients may be that T4 monotherapy of hypothyroidism often requires TSH-suppressive doses of T4 for symptom elimination [34–36], which overlap with symptoms of CKD (fatigue, memory and mood changes). T4/T3 combination therapy may therefore be a superior treatment regime for CKD patients since it mimics thyroid function tests of healthy controls best and leads to more favourable changes in serum cholesterol, N-terminal pro b-type natriuretic peptide, sex hormone–binding globulin and procollagen type I N-terminal propeptide, thereby indicating a more euthyroid state in peripheral target tissues [37]. This may be of special interest in CKD patients since, for example, cholesterol is one of the target modifiable markers in CVD management [38].

In our study, we detected an association of lower FT3 levels and low-FT3 syndrome with lower eGFR cross-sectionally, validating the reported associations of low T3 levels and low-FT3 syndrome with declining eGFR [14, 39] from two smaller retrospective studies of patients with severely reduced eGFR and ESKD. Other cross-sectional findings are mostly available from population-based studies and indicate an association between higher TSH levels or hypothyroidism with lower eGFR [9, 29, 40, 41], which we did not observe in our cohort. Pathophysiological mechanisms contributing to all of the above associations have been reported for advanced CKD and are diverse, including a reduced peripheral deiodinase activity [42], drugs (amiodarone, steroids, β-blockers) [43, 44], accumulation of inorganic iodide and uraemic toxins in combination with chronic metabolic acidosis [45]. We tried to account for these factors wherever possible in the GCKD study (amiodarone use); nonetheless, these factors already seem to play an essential role in patients with moderate CKD.

Since T3 has been reported as a strong marker of survival in uraemic patients, we evaluated the effect size of FT3 and other thyroid traits on all-cause mortality in CKD patients. Yang et al. [46] detected a more reliable association of low T3 levels with mortality than FT4 in a small ($n = 211$), South Korean, CKD Stage 4 cohort with overt proteinuria, consistent with our findings. Rhee et al. [29] investigated the association of TSH levels and risk of death among 227 422 US veterans with Stage 3 CKD, but FT3 levels were not measured. Here, high-normal and lower TSH levels were associated with a higher risk of death. In our study, we were able to analyse a full set of thyroid hormone markers with mortality for patients with moderate CKD. We were able to detect a significant association of lower FT3 and higher FT4 levels with all-cause mortality, but not TSH. Future interventional studies could clarify the potential benefits of T3 replacement therapy on mortality, especially since conversion of T4 to T3 and the compensatory increase of TSH is impaired in CKD and uraemia [47].

There are conflicting results on the longitudinal effect of hypothyroidism, hyperthyroidism, low-FT3 syndrome and thyroid hormones on eGFR. Some authors reported a negative impact of hypothyroidism on eGFR [9, 48], but other investigators reported that hypothyroidism could be described as rather beneficial for the progression of CKD [41, 49, 50]. In experimental animal models, long-term hyperthyroidism may lead to incident CKD or CKD progression [51]. Here, low T3 might serve as an adaptive mechanism in order to slow the progression and the consequences of CKD, but treatment of hypothyroidism in CKD patients improves eGFR, renal function [52] and renal graft

function [53]. Fan *et al.* [14] suggested low-T3 syndrome to be a predictor of CKD progression. To clarify some of the raised issues, especially for patients with moderate CKD, we set out to analyse the association of a full panel of thyroid hormones with eGFR and adverse renal events. In the GCKD study we were able to detect higher UACR values for hypothyroid patients compared with euthyroid patients, but the association of low-FT3 syndrome with hypothyroidism was only nominally significant, most likely due to small case numbers for hypothyroidism. But we were able to detect a highly significant association of lower FT3 levels, hypothyroidism and low-FT3 syndrome with a higher risk of developing adverse renal events over time, emphasizing the negative impact of low thyroid function on renal function and adverse renal events, even in the early stages of CKD, despite higher comorbidity rates for low-FT3 syndrome patients, who may have other factors influencing this association, such as infections. It should be noted that T4 monotherapy is associated with low serum T3 levels and CKD patients are known to have reduced iodothyronine deiodinase 2 (DIO2) activity [42], further impairing peripheral conversion of T4 to T3. Moreover, the well-known *DIO2* Thr92Ala single nucleotide polymorphism has a higher prevalence in hypothyroid patients (11.3%) than in the general population (10.7%) [54] and reduces DIO2 activity and serum levels of T3 in thyroid-deficient patients [55], a status that may hold true for CKD patients. These issues might be resolved by prescription of T3–T4 combination therapy [37]. Hoever, trials in population-based studies were unable to show a superiority of combination therapy versus T4 monotherapy [34–36], but no trials have been conducted for CKD patients so far to clarify if this high-risk subpopulation may benefit from T3–T4 combination therapy.

The strengths of our study include its large sample size of CKD patients in an early phase of their disease course with a homogeneous ethnic background under standard nephrologist care, ensuring a homogeneously treated, statistically powerful cohort, as well as the use of standardized questionnaires to collect all information and a standardized event abstraction process, which reduces heterogeneity, the collection of detailed medication information, a full thyroid marker panel and a reliable estimation of all biomarker measurements in certified laboratories.

Our study has some limitations. The reported estimates of the effects of TFMs on the different outcomes may still be biased due to residual confounding in the absence of knowledge and data not available in the GCKD study, such as dietary iodine, chronic inflammation, protein-energy wasting and malnutrition. Furthermore, our results may not be generalizable to other populations of different ethnicity or patients with normal or highly reduced eGFR. Finally, repeated measurements of TFMs over time were not available to study time-varying effects.

In summary, patients with mild to moderate CKD suffering from a high prevalence of thyroid function abnormalities are at an increased risk of adverse renal events and all-cause mortality over time.

SUPPLEMENTARY DATA

Supplementary data are available at ckj online.

ACKNOWLEDGEMENTS

FUNDING

AUTHORS' CONTRIBUTIONS

S.B.A., E.S., K.U.E. and A.K. were involved in the study conception. U.T.S., S.B.A., E.S., K.U.E. and A.K. were involved in the study design. U.T.S., M.N., M.P.S., F.K., S.B.A., E.S., K.U.E. and A.K. were involved in data acquisition. U.T.S., I.S. and P.S. were involved in data analysis. U.T.S., I.S., F.K., K.U.E., A.K. and P.S. were involved in data interpretation. U.T.S., I.S., M.N., M.P.S., F.K., S.B.A., E.S., K.U.E., A.K. and P.S. provided critical intellectual input. U.T.S., I.S., F.K., A.K. and P.S. drafted the article. U.T.S., I.S., M.N., M.P.S., F.K., S.B.A., E.S., K.U.E., A.K. and P.S. provided critical revision of the article.

CONFLICT OF INTEREST STATEMENT

E.S. has received honoria for lectures from Fresenius Kabi and Siemens. All other authors have nothing to declare. The results presented in this article have not been published previously in whole or part, except in abstract format.

REFERENCES

1. Levin A, Tonelli M, Bonventre J *et al.* Global kidney health 2017 and beyond: a roadmap for closing gaps in care, research, and policy. *Lancet* 2017; 390: 1888–1917
2. Eckardt KU, Coresh J, Devuyst O *et al.* Evolving importance of kidney disease: from subspecialty to global health burden. *Lancet* 2013; 382: 158–169
3. Chonchol M, Lippi G, Salvagno G *et al.* Prevalence of subclinical hypothyroidism in patients with chronic kidney disease. *Clin J Am Soc Nephrol* 2008; 3: 1296–1300
4. Kaptein EM. Thyroid hormone metabolism and thyroid diseases in chronic renal failure. *Endocr Rev* 1996; 17: 45–63
5. Kaptein EM, Quion-Verde H, Chooljian CJ *et al.* The thyroid in end-stage renal disease. *Medicine (Baltimore)* 1988; 67: 187–197
6. Lo JC, Chertow GM, Go AS *et al.* Increased prevalence of subclinical and clinical hypothyroidism in persons with chronic kidney disease. *Kidney Int* 2005; 67: 1047–1052
7. Ng YY, Wu SC, Lin HD *et al.* Prevalence of clinical and subclinical thyroid disease in a peritoneal dialysis population. *Perit Dial Int* 2012; 32: 86–93
8. Hollowell JG, Staehling NW, Flanders WD *et al.* Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). *J Clin Endocrinol Metab* 2002; 87: 489–499
9. Schultheiss UT, Daya N, Grams ME *et al.* Thyroid function, reduced kidney function and incident chronic kidney disease in a community-based population: the Atherosclerosis Risk in Communities study. *Nephrol Dial Transplant* 2016; 32: 1874–1881.
10. Xu G, Yan W, Li J. An update for the controversies and hypotheses of regulating nonthyroidal illness syndrome in chronic kidney diseases. *Clin Exp Nephrol* 2014; 18: 837–843
11. Rhee CM, Kim S, Gillen DL *et al.* Association of thyroid functional disease with mortality in a national cohort of incident hemodialysis patients. *J Clin Endocrinol Metab* 2015; 100: 1386–1395
12. Moon S, Kim MJ, Yu JM *et al.* Subclinical hypothyroidism and the risk of cardiovascular disease and all-cause mortality: a meta-analysis of prospective cohort studies. *Thyroid* 2018; 28: 1101–1110
13. Zoccali C, Mallamaci F, Tripepi G *et al.* Low triiodothyronine and survival in end-stage renal disease. *Kidney Int* 2006; 70: 523–528
14. Fan J, Yan P, Wang Y *et al.* Prevalence and clinical significance of low T3 syndrome in non-dialysis patients with chronic kidney disease. *Med Sci Monit* 2016; 22: 1171–1179
15. Meuwese CL, Carrero JJ. Chronic kidney disease and hypothalamic-pituitary axis dysfunction: the chicken or the egg? *Arch Med Res* 2013; 44: 591–600
16. Eckardt KU, Barthlein B, Baid-Agrawal S *et al.* The German Chronic Kidney Disease (GCKD) study: design and methods. *Nephrol Dial Transplant* 2012; 27: 1454–1460
17. Titze S, Schmid M, Kottgen A *et al.* Disease burden and risk profile in referred patients with moderate chronic kidney disease: composition of the German Chronic Kidney Disease (GCKD) cohort. *Nephrol Dial Transplant* 2015; 30: 441–451
18. Levey AS, Stevens LA, Schmid CH *et al.* A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009; 150: 604–612
19. Ittermann T, Khattak RM, Nauck M *et al.* Shift of the TSH reference range with improved iodine supply in northeast Germany. *Eur J Endocrinol* 2015; 172: 261–267
20. Meisinger C, Ittermann T, Wallaschofski H *et al.* Geographic variations in the frequency of thyroid disorders and thyroid peroxidase antibodies in persons without former thyroid disease within Germany. *Eur J Endocrinol* 2012; 167: 363–371
21. Khattak RM, Ittermann T, Nauck M *et al.* Monitoring the prevalence of thyroid disorders in the adult population of northeast Germany. *Popul Health Metrics* 2016; 14: 39
22. Section 2: AKI Definition. *Kidney Int Suppl* 2012; 2: 19–36
23. Collet D. *Modelling Survival Data in Medical Research.* London: Chapman and Hall/CRC, 2003
24. Austin PC, Lee DS, Fine JP. Introduction to the analysis of survival data in the presence of competing risks. *Circulation* 2016; 133: 601–609
25. Austin PC, Fine JP. Practical recommendations for reporting Fine-Gray model analyses for competing risk data. *Stat Med* 2017; 36: 4391–4400
26. Azur MJ, Stuart EA, Frangakis C *et al.* Multiple imputation by chained equations: what is it and how does it work? *Int J Methods Psychiatr Res* 2011; 20: 40–49
27. Wavamunno MD, Harris DC. The need for early nephrology referral. *Kidney Int Suppl* 2005; 67: S128–S132
28. Rucker D, Hemmelgarn BR, Lin M *et al.* Quality of care and mortality are worse in chronic kidney disease patients living in remote areas. *Kidney Int* 2011; 79: 210–217
29. Rhee CM, Kalantar-Zadeh K, Streja E *et al.* The relationship between thyroid function and estimated glomerular filtration rate in patients with chronic kidney disease. *Nephrol Dial Transplant* 2015; 30: 282–287
30. Mohamedali M, Reddy Maddika S, Vyas A *et al.* Thyroid disorders and chronic kidney disease. *Int J Nephrol* 2014; 2014: 1–6
31. Volzke H, Alte D, Kohlmann T *et al.* Reference intervals of serum thyroid function tests in a previously iodine-deficient area. *Thyroid* 2005; 15: 279–285
32. Volzke H, Ittermann T, Schmidt CO *et al.* Subclinical hyperthyroidism and blood pressure in a population-based prospective cohort study. *Eur J Endocrinol* 2009; 161: 615–621
33. Klein I, Ojamaa K. Thyroid hormone and the cardiovascular system. *N Engl J Med* 2001; 344: 501–509

34. Wiersinga WM. T4 + T3 combination therapy: any progress. *Endocrine* 2019; 66: 70–78

35. Wiersinga WM. Therapy of endocrine disease: T4 + T3 combination therapy: is there a true effect? *Eur J Endocrinol* 2017; 177: R287–R296

36. Wiersinga WM, Duntas L, Fadeyev V *et al*. 2012 ETA guidelines: the use of L-T4 + L-T3 in the treatment of hypothyroidism. *Eur Thyroid J* 2012; 1: 55–71

37. Fadeyev VV, Morgunova TB, Melnichenko GA *et al*. Combined therapy with L-thyroxine and L-triiodothyronine compared to L-thyroxine alone in the treatment of primary hypothyroidism. *Hormones (Athens)* 2010; 9: 245–252

38. Thompson S, James M, Wiebe N *et al*. Cause of death in patients with reduced kidney function. *J Am Soc Nephrol* 2015; 26: 2504–2511

39. Song SH, Kwak IS, Lee DW *et al*. The prevalence of low triiodothyronine according to the stage of chronic kidney disease in subjects with a normal thyroid-stimulating hormone. *Nephrol Dial Transplant* 2009; 24: 1534–1538

40. Asvold BO, Bjoro T, Vatten LJ. Association of thyroid function with estimated glomerular filtration rate in a population-based study: the HUNT study. *Eur J Endocrinol* 2011; 164: 101–105

41. Chaker L, Sedaghat S, Hoorn EJ *et al*. The association of thyroid function and the risk of kidney function decline: a population-based cohort study. *Eur J Endocrinol* 2016; 175: 653–660

42. Lim VS, Passo C, Murata Y *et al*. Reduced triiodothyronine content in liver but not pituitary of the uremic rat model: demonstration of changes compatible with thyroid hormone deficiency in liver only. *Endocrinology* 1984; 114: 280–286

43. Iglesias P, Diez JJ. Thyroid dysfunction and kidney disease. *Eur J Endocrinol* 2009; 160: 503–515

44. Carrero JJ, Qureshi AR, Axelsson J *et al*. Clinical and biochemical implications of low thyroid hormone levels (total and free forms) in euthyroid patients with chronic kidney disease. *J Intern Med* 2007; 262: 690–701

45. Dousdampanis P, Trigka K, Vagenakis GA *et al*. The thyroid and the kidney: a complex interplay in health and disease. *Int J Artif Organs* 2014; 37: 1–12

46. Yang JW, Han ST, Song SH *et al*. Serum T3 level can predict cardiovascular events and all-cause mortality rates in CKD patients with proteinuria. *Ren Fail* 2012; 34: 364–372

47. Koenig RJ. Modeling the nonthyroidal illness syndrome. *Curr Opin Endocrinol Diabetes Obes* 2008; 15: 466–469

48. Meuwese CL, Gussekloo J, de Craen AJ *et al*. Thyroid status and renal function in older persons in the general population. *J Clin Endocrinol Metab* 2014; 99: 2689–2696

49. Conger JD, Falk SA, Gillum DM. The protective mechanism of thyroidectomy in a rat model of chronic renal failure. *Am J Kidney Dis* 1989; 13: 217–225

50. Tomford RC, Karlinsky ML, Buddington B *et al*. Effect of thyroparathyroidectomy and parathyroidectomy on renal function and the nephrotic syndrome in rat nephrotoxic serum nephritis. *J Clin Invest* 1981; 68: 655–664

51. van Hoek I, Daminet S. Interactions between thyroid and kidney function in pathological conditions of these organ systems: a review. *Gen Comp Endocrinol* 2009; 160: 205–215

52. Shin DH, Lee MJ, Kim SJ *et al*. Preservation of renal function by thyroid hormone replacement therapy in chronic kidney disease patients with subclinical hypothyroidism. *J Clin Endocrinol Metab* 2012; 97: 2732–2740

53. Reinhardt W, Misch C, Jockenhovel F *et al*. Triiodothyronine (T3) reflects renal graft function after renal transplantation. *Clin Endocrinol (Oxf)* 1997; 46: 563–569

54. Wouters HJ, van Loon HC, van der Klauw MM *et al*. No effect of the Thr92Ala polymorphism of deiodinase-2 on thyroid hormone parameters, health-related quality of life, and cognitive functioning in a large population-based cohort study. *Thyroid* 2017; 27: 147–155

55. Castagna MG, Dentice M, Cantara S *et al*. DIO2 Thr92Ala reduces deiodinase-2 activity and serum-T3 levels in thyroid-deficient patients. *J Clin Endocrinol Metab* 2017; 102: 1623–1630