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Nontraditional cardiovascular risk factors in end-stage renal disease : studies on inflammatory markers and thyroid hormones

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Chapter 7

Non-thyroidal illness: a risk factor for coronary calcification and arterial stiffness in patients undergoing peritoneal dialysis?

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Abstract

Objectives: Low triiodothyronine levels, as part of the non-thyroidal illness syndrome, are common in dialysis patients and have repeatedly been shown to be associated with increased (cardiovascular) mortality rates. We hypothesized that increased vascular calcification may intermediate this relationship.

Methods: A total of 84 patients from the Stockholm region receiving maintenance peritoneal dialysis were included in the study. Serum concentrations of free triiodothyronine (*fT3*), thyroxine and thyroid stimulating hormone were measured. Coronary artery calcium (*CAC*) scores were assessed by cardiac computed tomography scans. Surrogates of arterial stiffness included aortic diastolic and systolic blood pressures, pulse pressure, augmentation pressure and Buckberg's subendocardial viability ratio measured by pulse waveform analyses. Patients were subsequently followed and events of death and censoring were recorded. Thyroid hormone concentrations were associated with *CAC* scores, measures of arterial stiffness and all-cause mortality. The associations between *CAC* scores and arterial stiffness surrogates and mortality were also determined to evaluate a possible causal pathway.

Results: Both *CAC* scores and arterial stiffness surrogates were substantially higher in individuals with low *fT3* levels. These associations persisted in multivariate logistic and linear regression analyses. During a median (interquartile range) follow-up of 32 (22–42) months, 24 patients died. Both *fT3* levels below the median value [HR crude 4.1, 95% confidence interval (CI) 1.4 to 12.6] and *CAC* scores above the median value (HR crude 5.8, 95% CI 1.7 to 20.1) were strongly associated with mortality.

Conclusions: In patients undergoing peritoneal dialysis, *fT3* levels were strongly associated with arterial stiffness, coronary artery calcification and mortality. We speculate that the association between non-thyroidal illness and mortality may be partly mediated by acceleration of vascular calcification.

Introduction

Coronary artery disease (*CAD*)¹ and myocardial ischaemia² frequently occur in patients with end-stage renal disease (*ESRD*), and are directly associated with increased risk of mortality.^{3,4} *CAD* in *ESRD* is characterized by media thickening (Mönckeberg media sclerosis) and heavily calcified plaques.⁵ Furthermore, cardiac valve calcification⁶ and systemic atherosclerosis⁷ are also common in patients with *ESRD*. Therefore it appears that uraemic risk factors, such as hyperphosphataemia, inflammation and depletion of vascular calcification inhibitors [fetuin-A and matrix gla protein (*MGP*)] may promote the calcification of the vasculature on a systemic level.

Thyroid hormone alterations due to chronic disease are frequently observed in *ESRD* and are characterized by low serum concentrations of triiodothyronine (*T3*) with normal thyroid-stimulating hormone (*TSH*) levels. This pattern is known as non-thyroidal illness,⁸ and its prevalence increases progressively with reduced renal function; it is found in approximately 70% of individuals with *ESRD*.^{8,9} A low *T3* level in patients with chronic kidney disease (*CKD*) has long been considered a benign compensatory response to malnutrition and wasting. However, recently, these abnormalities have been associated with a two- to three-fold elevated mortality rate in patients undergoing haemodialysis (*HD*)¹⁰⁻¹² or peritoneal dialysis (*PD*).¹³ This excess mortality risk seemed to be most specific for cardiovascular causes.¹¹

Whether a low *T3* concentration in *ESRD* is causally implicated in the high cardiovascular disease risk of *CKD* is still unknown, but an accelerated rate of atherosclerosis represents a potential mechanism. In support of this, free *T3* (*fT3*) levels were negatively associated with carotid artery intima-media thickness, arterial stiffness and pulse wave velocity in 137 non-diabetic *HD* patients.⁹ In patients undergoing *PD*, an inverse association was described between *fT3* levels and arterial stiffness.¹⁴ In addition, non-thyroidal illness has been implicated in uraemic endothelial dysfunction,^{15,16} and dyslipidaemia.¹⁷ This is further supported by the demonstration of overt and subclinical hypothyroidism as true cardiovascular disease risk factors in the community.^{18,19}

Thus, the aim of this study was to test the hypothesis that vascular calcification mediates the effect of non-thyroidal illness on mortality. To assess vascular calcification, we performed non-contrast cardiac computed tomography (*CT*) and pulse wave-form analyses in a cohort of prevalent patients undergoing maintenance *PD*.

Methods and materials

Study population

We conducted a longitudinal follow-up study in a cohort of prevalent *PD* patients from the Stockholm region. This cohort was originally designed to investigate inflammatory marker variability over time. Subjects were recruited between March 2008 and April 2011. All patients who were receiving *PD* therapy in the Stockholm region were invited to participate (n=164).

Of these, 55 patients did not provide informed consent, six underwent transplantation, two died, eight switched to haemodialysis and nine were excluded because of medical conditions (including mental disorders) that precluded their entry into the study. Measurements were performed weekly during a period of 3 months in the remaining 84 patients. The causes of ESRD in these patients were diabetes mellitus (n=10), renovascular disease (n=10), glomerulonephritis (n=5), immunoglobulin A nephropathy (n=6) and other (n=20), or unknown (n=33). From inclusion onwards, events of death and censoring due to the end of follow-up or renal transplantation were recorded. Comorbidity was scored based on the 7-point scale of Davies et al.²⁰ simplified into a three-category comorbidity risk scale (low, medium and high). Nutritional status was evaluated using subjective global assessment (SGA) according to the method of Detsky et al.²¹ Among all patients, 60 (71%) used beta-blockers and 27 (32%) calcium antagonists. In addition, 47 subjects (56%) used angiotensin-converting enzyme inhibitors or angiotensin antagonists and 65 (77%) and 19 (23%) were receiving alfacalcidol and calcitriol, respectively. The study protocol was approved by the Ethics Committee of Karolinska Institutet at Huddinge University Hospital (Stockholm, Sweden) and informed consent was obtained from all patients.

Arterial stiffness

In 74 patients, central aortic pressure waveforms were recorded by applanation tonometry at the radial site using a SphygmoCor device (AtCor Medical, Sidney, Australia). The methodology utilizes a validated transfer function that creates aortic pressure wave shapes on the basis of 20 sequential peripheral arterial waveforms.^{22,23} In this way, aortic systolic and diastolic pressures were derived. Aortic pulse pressure was calculated by subtracting the central diastolic from the systolic blood pressure (BP). The difference between the first and second systolic peaks of the aortic waveform defined the aortic augmentation pressure. Patients with a negative aortic augmentation pressure were considered to have a value of 0 mmHg in the analysis. Buckberg's subendocardial viability ratio (SEVR) was calculated by dividing the diastolic by the systolic pressure time index. An experienced nurse performed the pulse waveform measurements in a temperature-controlled room, with patients in a supine position after resting for 5 min to acclimatize.

Cardiac CT protocol and coronary artery calcium score measurements

In 66 patients, cardiac CT scans were performed using an electrocardiogram (ECG)-gated technique on a 64-channel detector scanner [LightSpeed VCT, General Electric (GE) Healthcare, Milwaukee, WI, USA] in cine mode. A standard non-contrast protocol was used with the following parameters: tube voltage 100 kV, tube current 200 mA, rotation time 350 ms, slice thickness 2.5 mm and displayed field of view 25 cm.

The data were transferred to a dedicated workstation (Advantage Workstation 4.4, GE Healthcare) for further processing and analysis using coronary artery calcium (CAC)-scoring software (Smart-score 4.0, GE Healthcare). A standard threshold of 130 Hounsfield units for identifying calcified plaque was adopted. CAC scores were expressed in Agatston units (AU) as previously described in

detail.²⁴ Total CAC score was calculated as the sum of the CAC scores in the left main artery, the left anterior descending artery, the left circumflex artery and the right coronary artery. CAC scores were expressed in percentiles with respect to the distribution for an age- and sex-matched reference population.²⁵

Biochemical measurements

Venous blood was collected after an overnight fast; all blood samples were centrifuged immediately and stored at -70°C until required for analysis. Serum high-sensitivity C-reactive protein (CRP), calcium, phosphate, creatinine, urea and albumin levels (bromocresol purple) were determined using routine methods at the Department of Laboratory Medicine, Karolinska University Hospital. Serum levels of IL-6 were quantified using an Immulite system (Siemens Healthcare Diagnostics, Los Angeles, CA, USA). Plasma analyses of thyroid hormones were performed using a Roche Modular E/Cobas E analyser and commercially available electrochemiluminescence immunoassays for fT3 [analytical sensitivity (AS), 0.4 pmol/L; total coefficients of variation (CVs), 6.27% and 3.36% at 3.16 and 10.03 pmol/L, respectively], fT4 (AS, 0.3 pmol/L; total CVs, 2.05% and 3.03% at 12.01 and 34.70 pmol/L, respectively) and TSH (AS, 0.014 mU/L; total CVs, 2.16% and 2.42% at 0.995 and 5.530 mU/L, respectively). Results are expressed as the average of two measurements. Residual glomerular filtration rate (rGFR) was calculated as previously reported and expressed in mL/min/1.73m².²⁶

Statistical analysis

Patient characteristics are presented across two fT3 strata (based on the median value) as means (SD or SEM), medians [interquartile range (IQR)] or percentages, and compared appropriately. Linear regression analyses were performed to study associations between thyroid hormones and measures of arterial stiffness. Due to non-normality, CAC scores were categorized and a linear trend of thyroid hormones across these categories was investigated using a polynomial linear term in one-way ANOVA. Additionally, logistic regression models were applied to quantify the effect of thyroid hormone levels on CAC scores, dichotomized at the median value (920 AU). Univariate and multivariate regression models were used for analyses. In the multivariate models, age, sex, dialysis vintage and Davies scores were considered as confounders. For this purpose, dialysis vintage was logarithmically transformed due to non-normality. For the models including thyroid hormones as exposure, SGA, which showed the strongest association with non-thyroidal illness and mortality, was added. Because thyroid hormone status could also influence cytokine production,²⁷ and we were restricted in the number of covariates due to our small sample size, inflammation was not included in the primary analyses. In a sensitivity analysis, however, we examined the results after adjustment for log(IL-6). Assumptions underlying linear and logistic regression analyses were tested and not found to be violated.

Survival was analysed using Kaplan–Meier methodology. Only in the plot, mortality follow-up was restricted to the point at which 20% of patients were still at risk (44 months).²⁸ Cox proportional hazards models were fitted on the whole follow-up period and used to calculate hazard ratios (HR). To anticipate the possibility of monotone likelihood due to small numbers of events, Cox models were re-run after applying a shrinkage factor according to a modified version of the Firth method.²⁹ The same confounders described above were included in multivariate Cox models.

Primary analyses were performed using SPSS 20 (IBM Inc., New York, NY, USA). SAS version 9.3 (SAS Campus Drive, Cary, NC, USA) was used for Cox models with inclusion of a shrinkage factor. In linear regression analyses, beta values with 95% confidence intervals (CIs) not including 0 and odds ratios with 95% CIs not including 1 were considered statistically significant. For all other tests, a P-value lower than 0.05 was considered to indicate statistical significance. Figures were created with Prism 5.02 (Graphpad, 1992).

Results

The study population consisted of 84 PD patients; 68% were men, 24% had diabetes and 19% were smokers. The mean (SD) age of participants was 63.7 (14.1) years. Subjects with serum fT3 levels below the median value (3.95 pmol/L) had a higher prevalence of diabetes and protein–energy wasting (**Table 1**), whereas those with relatively low fT3 levels tended to have lower haemoglobin and albumin levels, lower rGFR but higher inflammatory biomarker levels (IL-6 and CRP). Mean serum calcium and phosphate levels and median dialysis vintage did not differ significantly between the fT3 groups.

Measures of arterial stiffness, including aortic systolic BP, pulse pressure and augmentation pressure were significantly higher in the group with low fT3 values (**Table 2**). Results from linear regression analyses (**Figure 1** and **Table 3**) showed statistically significant univariate associations between fT3 and aortic systolic BP, pulse pressure, augmentation pressure and SEVR. After adjustment for confounders, beta values remained statistically significant for aortic systolic BP, pulse pressure and augmentation pressure. A trend remained for the association between fT3 and SEVR, which was not different when heart rate and systolic BP were excluded from the analyses. Log(TSH) was strongly associated with aortic pulse pressure (β 17.7, 95% CI 5.2 to 30.2), aortic augmentation pressure (β 7.1, 95% CI 1.2 to 13.0) and SEVR (β -20.1, 95% CI -38.5 to -1.7). Adjustment for log(IL-6) levels did not significantly alter the results.

The majority of the patients had CAC scores above 1000 AU. Calcification affected all three coronary vessels in almost all patients. Compared to age- and sex-specific distributions among the general population 25, 73% of study subjects had CAC scores above the 90th percentile. As presented in **Table 2**, median total CAC scores were significantly higher in subjects with low versus high fT3 levels [1527, interquartile range (IQR) 594–2507 vs. 438, IQR 56–1824; $P = 0.01$]; this relationship was also true for the different coronary arteries separately. Conversely, fT3 levels showed a gradual decline across CAC categories (P for trend = 0.001). In logistic regression analyses (**Table 3**), the

Table 1. Baseline characteristics of the 84 prevalent PD patients according to median values of free triiodo thyronine (fT3)

	Low fT3 group ≤3.95 pmol/L n = 42		High fT3 group >3.95 pmol/L n = 42		p-value
<i>General characteristics</i>					
Men, % ¹	60		76		0.10
Age, years ²	65 (13)		62 (15)		0.33
Patients with medium/high Davies score, % ¹	55/21		60/7		0.15
Diabetes mellitus, % ¹	31		17		0.08
Protein–energy wasting, % ^{1,4}	50		30		0.09
Dialysis vintage, months ^c	15 (7 to 32)		11 (6 to 21)		0.44
CAPD, % ^{1,5}	78.6		76.2		0.794
<i>Laboratory measurements</i>					
Creatinine, mmol/L ²	738 (168)		710 (181)		0.46
Residual eGFR, mL/min/1.73m ^{3,3}	2.3 (1.0 to 3.2)		3.2 (2.1 to 5.8)		0.008
Albumin, g/L ²	29.5 (4.6)		33.2 (3.9)		<0.0001
Haemoglobin, mmol/L ²	116 (12)		121 (10)		0.04
IL-6, pg/L ³	8.2 (4.9 to 17.2)		5.1 (2.8 to 7.6)		0.001
C-reactive protein, mg/L ³	5.2 (1.7 to 19.9)		3.3 (0.9 to 7.1)		0.05
TSH, mIU/L ³	2.1 (1.3 to 3.2)		2.2 (1.4 to 3.1)		0.72
fT3, pmol/L ²	3.4 (0.3)		4.5 (0.4)		-
fT4, pmol/L ²	12.8 (2.5)		13.8 (3.5)		0.12
Calcium, mmol/L ²	2.3 (0.2)		2.3 (0.2)		0.31
Phosphate, mmol/L ²	1.7 (0.6)		1.7 (0.4)		0.54

1. Differences between groups for categorical data were tested by chi-squared test.
2. Data are expressed as mean (SD); differences between groups were tested using an independent sample t-test.
3. Data are expressed as median (interquartile range); differences between groups were tested by the Mann–Whitney U test.
4. Protein–energy wasting defined as subjective global assessment score >1.
5. The remaining patients underwent automated peritoneal dialysis.

TSH, thyroid-stimulating hormone; fT4, free thyroxine; CAPD, continuous ambulatory peritoneal dialysis; eGFR, estimated glomerular filtration rate.

risk of having a CAC score >920 AU was higher in those with low versus high fT3 levels [odds ratio (OR) 3.4, 95% CI 1.2 to 9.4], an association that persisted after adjustment for confounders. After adjustment for log(IL-6), point estimates remained approximately the same while the confidence interval broadened substantially (OR 3.4, 95% CI 0.7 to 15.7). During a median (IQR) follow-up of 32 (22–42) months, a total of 24 (29%) patients died. Of these deaths, 17 (41%) and seven (17%) occurred in the low and high fT3 groups, respectively (Fig. 2). In crude analyses, individuals in the low fT3 group had a higher mortality risk (HR 4.1, 95% CI 1.4 to 12.6) than those with high fT3 levels (**Table 4**). The point estimate was reduced after adjustment for confounders and even further after adjustment for CAC categories. Regarding to the association between CAC scores and mortality, 15 (46%) subjects died in the group with CAC scores >920 AU as compared

to three (9%) patients with CAC scores ≤ 920 AU. The high CAC group had higher risks of death in both crude (HR 5.8, 95% CI 1.7 to 20.1) and adjusted (HR 5.6, 95% CI 1.4 to 22.9) Cox models. After applying a shrinkage factor to the Cox models, the associations between low fT3 and mortality (crude HR 2.6, 95% CI 1.2 to 6.6; adjusted HR 1.9, 95% CI 0.8 to 5.1) and between high CAC scores and mortality (crude HR 5.2, 95% CI 1.8 to 19.8; adjusted HR 4.5, 95% CI 1.3 to 20.0) remained. Measures of arterial stiffness were not associated with mortality (data not shown). Thyroid hormone levels did not differ between those who used or did not use beta-blockers (data not shown). Patients undergoing continuous ambulatory PD were not significantly different from those undergoing automated PD with respect to demographic characteristics, thyroid hormone levels, total CAC scores and mortality (data not shown). Finally, demographic characteristics, thyroid status and survival were not significantly different in patients who did and did not undergo cardiac CT scanning (data not shown).

Table 2. Coronary artery calcium (CAC) scores and measures of arterial stiffness according to median free triiodothyronine (fT3) values

	Low fT3 group ≤ 3.95 pmol/L		High fT3 group > 3.95 pmol/L		p-value
<i>Pulse waveform analyses</i>	<i>n</i> = 38		<i>n</i> = 38		
Aortic systolic BP, mmHg ¹	134	(4)	120	(3)	0.005
Aortic diastolic BP, mmHg ¹	82	(2)	81	(2)	0.57
Aortic PP, mmHg ¹	52	(3)	40	(2)	0.006
Aortic AP, mmHg ¹	15	(1)	10	(1)	0.15
SEVR, % ¹	132	(5)	138	(4)	0.001
<i>Coronary CT scans</i>	<i>n</i> = 33		<i>n</i> = 33		
Total CAC score ²	1527	(594–2507)	438	(56–1824)	0.01
LM CAC score ²	70	(0–166)	22	(0–99)	0.41
LAD CAC score ²	655	(203–1109)	194	(46–594)	0.002
LCx CAC score ²	197	(74–617)	45	(0–269)	0.02
RCA CAC score ²	339	(86–900)	33	(0–734)	0.04

1. Data are expressed as mean (SEM); differences between groups were tested with one-way ANOVA.

2. Data are expressed as median (IQR); differences between groups were tested using the Kruskal–Wallis test.

BP, blood pressure; PP, pulse pressure; AP, augmentation pressure; SEVR, subendocardial viability ratio; CT, computed tomography; CAC, coronary artery calcium; LM, left main stem; LAD, left anterior descending; LCx left circumflex; RCA, right coronary artery.

Figure 1. Association between free triiodothyronine (fT3) and aortic systolic blood pressure (BP) (A), pulse pressure (PP) (B), augmentation pressure (AP) (C) and subendocardial viability ratio (SEVR) (D)

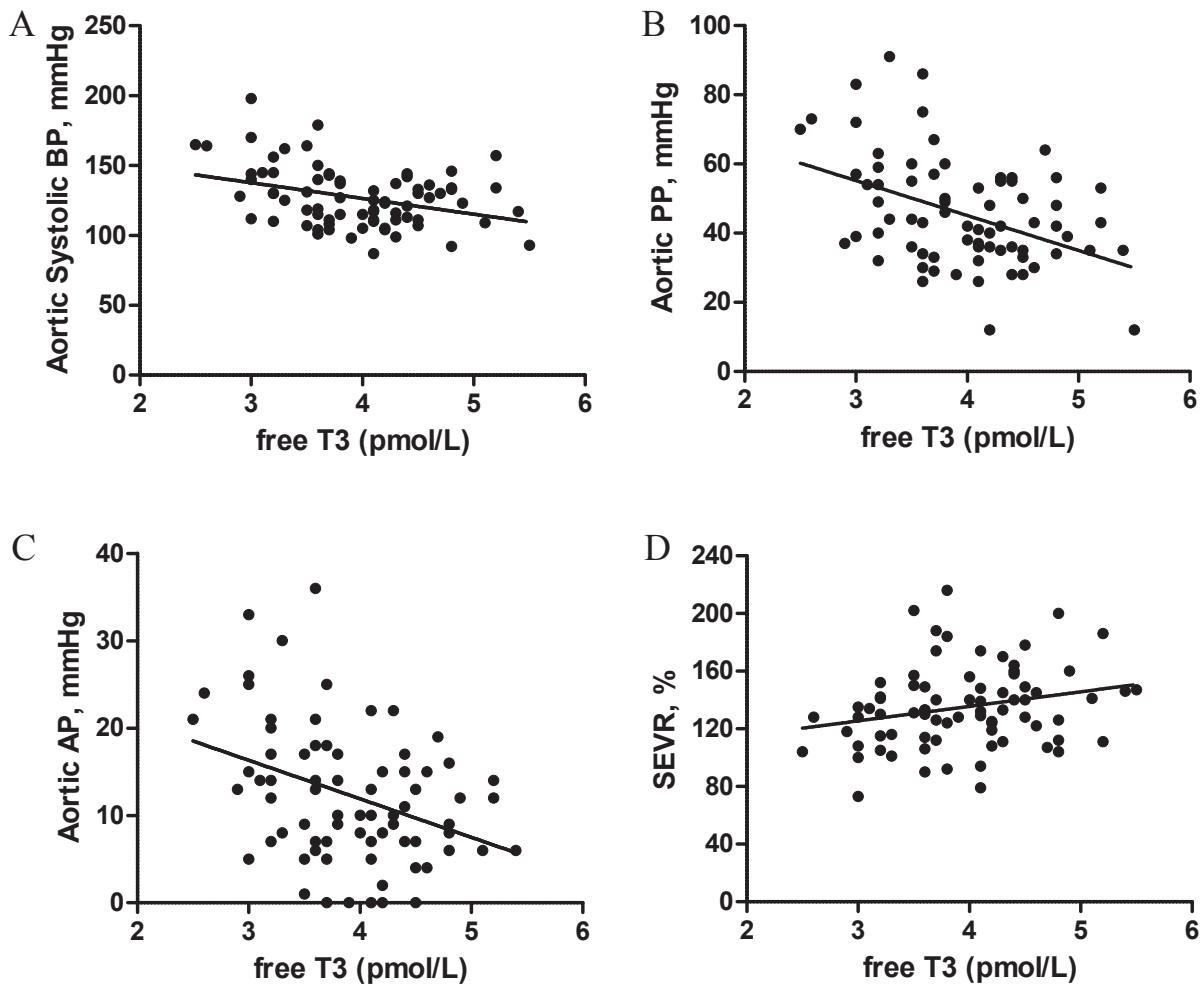


Table 3. Regression analyses of associations between serum free triiodothyronine (fT3) levels and coronary artery calcium (CAC) scores and measures of arterial stiffness

			Crude		Adjusted ²	
Logistic regression	Low fT3 - CAC score ¹	OR (95%CI)	3.4	(1.2 to 9.4)	4.5	(1.1 to 19.1)
Linear regression	fT3- Aortic systolic BP	β (95% CI)	-11.3	(-18.2 to -4.3)	-11.8	(-19.1 to -4.4)
	fT3- Aortic diastolic BP	β (95% CI)	-1.2	(-5.5 to 3.2)	-2.3	(-6.8 to 2.2)
	fT3- Aortic PP	β (95% CI)	-10.1	(-15.1 to -5.1)	-9.4	(-14.6 to -4.3)
	fT3- Aortic AP	β (95% CI)	-4.4	(-7.0 to -1.8)	-3.1	(-5.7 to -0.5)
	fT3- SEVR	β (95% CI)	10.1	(0.6 to 19.6)	7.5	(-0.7 to 15.8)

1. fT3 levels and CAC scores were dichotomized according to the median values (3.95 pmol/L and 920 Agatston units, respectively); for fT3, the highest group served as the reference.
 2. Adjusted for age, gender, Davies comorbidity score, log (dialysis vintage) and SGA. The association between fT3 and SEVR was additionally adjusted for heart rate and systolic blood pressure.
- BP, blood pressure; SEVR, subendocardial viability ratio; PP, pulse pressure; AP, augmentation pressure; SGA, subjective global assessment; OR, odds ratio; CI, confidence interval.

Discussion

In the present study, we found that serum fT3 levels were associated with measures of coronary calcification and arterial stiffness. Both fT3 and CAC, but not arterial stiffness, were associated with mortality. As 73% of our patients had CAC scores above the 90th percentile of age- and sex-specific distributions from the general population,²⁵ our data confirm previous findings that this patient population is subject to accelerated vascular calcification. CAC scores above 400 AU in the general population are considered to increase the short-term risk of cardiovascular events and death.³⁰ Compared to other PD^{31,32} and HD³³ populations, the CAC scores in our cohort were considerably higher. This may be due to the fact that CAC scores increase with age^{34,35}, and our group of prevalent patients were on average 10 years older than in the previous studies.^{31–33}

Figure 2. Kaplan–Meier survival curves according to free triiodothyronine (fT3) (A) and coronary artery calcium (CAC) score (B) categories

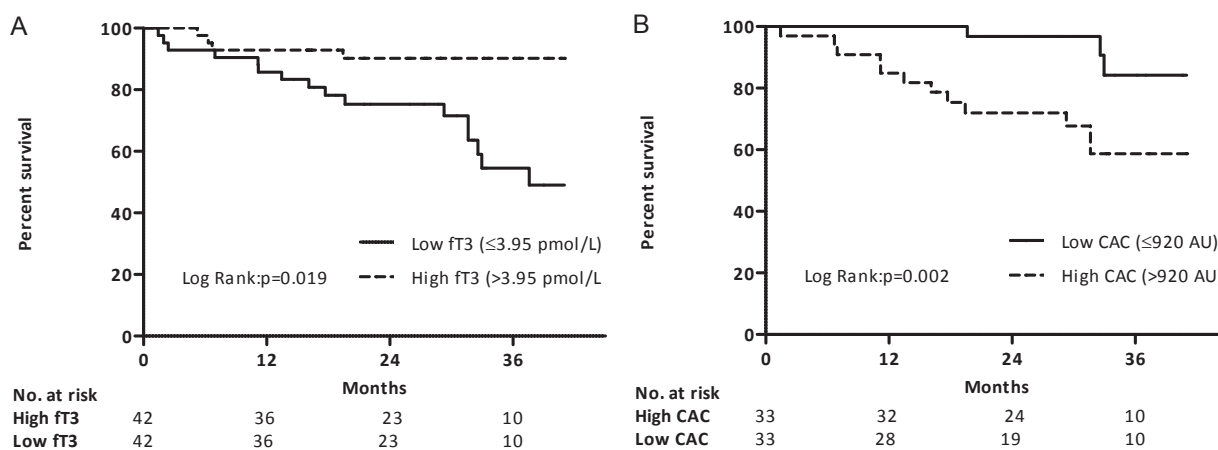


Table 4. Cox regression analyses of the association between free triiodothyronine (fT3) and coronary artery calcium (CAC) scores and mortality

Exposure ¹	Crude HR (95% CI)	Adjusted ² HR (95% CI)	Adjusted ³ HR (95% CI)
Low fT3	4.1 (1.4–12.6)	3.1 (0.9–10.1)	2.4 (0.7–8.6)
High CAC	5.8 (1.7–20.1)	5.6 (1.4–22.9)	-

1. Exposures were dichotomized according to the median value. The complementary group served as the reference group.
2. Adjusted for age, sex, log(dialysis vintage) and Davies comorbidity score. The association between fT3 and mortality was additionally adjusted for SGA (see Methods).
3. Additionally adjusted for CAC score categories.

SGA, subjective global assessment; HR, hazard ratio; CI, confidence interval.

The chief finding of the present study is an inverse association between serum fT3 levels and CAC scores. Notably, this association remained in multivariate models including SGA and IL-6 levels, suggesting an association independent of the protein–energy wasting syndrome. Our results partially agree with the observation in HD patients of an inverse association between fT3 and CAC scores; however, this correlation did not remain after multivariate adjustment.⁹ The approach of covariate selection may, however, have resulted in adjustment within the causal pathway in the previous study and could explain this divergence in results. Our finding of an inverse association between fT3 and measures of arterial stiffness agrees with the results of other studies in PD¹⁴ and HD patients⁹ also supporting a role of adverse effects of non-thyroidal illness on the systemic vasculature. Findings of studies in the general population suggest that overt and subclinical hypothyroidism are both true cardiovascular disease risk factors.^{18,19} Four possible mechanisms might explain how a low T3 milieu could augment atherosclerosis and vascular calcification. First, a low T3 state in ESRD has been linked to dyslipidaemia, which is reversible after thyroid hormone replacement.¹⁷ Secondly, non-thyroidal illness is associated with endothelial dysfunction,^{15,16} and promotes vasoconstriction by a direct effect on vascular smooth muscle cells.³⁶ Thirdly, in agreement with previous studies in non-renal patient,³⁷ our data show that non-thyroidal illness is associated with inflammation, which may be indirectly related to low T3 levels, vascular calcification and cardiovascular death via low fetuin-A levels.³⁸ Finally, *ex vivo* studies have demonstrated that the expression of Klotho³⁹ and MGP⁴⁰ are T3 dependent. The finding of Mizuno et al.³⁹ that T3 significantly increased the expression levels of the membrane form of the klotho gene is of interest as premature ageing and vascular calcification are prominent features of the uraemic phenotype.⁴¹ Moreover, the observation by Sato et al.⁴⁰ that physiological concentrations of T3 facilitate MGP gene expression in smooth muscle indicates that thyroid hormone replacement may be a future option to treat vascular calcification. Indeed, 45 years ago it was already known that cretinism was associated with vascular calcification, especially in patients who did not receive sufficient thyroid hormone replacement.⁴² The fact that thyroid hormones regulate skeletal development and synthesis and secretion of vitamin K-dependent proteins⁴³ may support an indirect link between non-thyroidal illness and vascular calcification.

The positive association between fT3 levels and mortality in our study is in agreement with an earlier report that mortality hazards were 3.2 times higher per 1 pg/L decrease in serum fT3 levels in 41 patients undergoing continuous ambulatory PD.¹³ Further, our results are consistent with findings in HD patients.¹⁰⁻¹² We previously showed that this association was predominantly accounted for by cardiovascular-specific deaths.¹¹ In agreement with previous data,^{3,4} our current analyses also illustrate that higher CAC scores were very strongly associated with consequent death. Although adjustment in a causal pathway may not be easy to interpret,⁴⁴ the effect estimate of the association between fT3 and mortality was reduced considerably after adjustment for CAC categories, suggesting a mediating role for coronary calcification. No association between measures of arterial stiffness and mortality was apparent. It is conceivable however that patients with high as well as those with low aortic BP, augmentation pressure and pulse pressure are at increased risk of death.

That is, low aortic augmentation and pulse pressures could reflect poor systolic left ventricular function. As pulse waveform analysis is less influenced by this phenomenon, Blacher et al.⁴⁵ were indeed able to show an association between this measure of arterial stiffness and subsequent mortality.

Some limitations should be acknowledged when interpreting our findings. Although our sample size and the number of events during follow-up were limited, associations remained strong and independent of confounders considered. Nevertheless, larger studies are indicated to verify our findings and to test whether non-thyroidal illness is linked to low levels of circulating inhibitors of vascular calcification, such as fetuin-A and MGP. Furthermore, the lack of CT data in 18 out of 84 patients could have resulted in a selection bias. However this is unlikely as demographic characteristics, thyroid status and survival were not different between responders and non-responders. It should also be acknowledged that, as we only assessed calcification in coronary arteries, we do not know whether non-thyroidal illness is also associated with increased calcification at other arterial sites. However, by inclusion of mortality follow-up data and the description of a biologically plausible causal chain, we do provide important evidence for this possibility. This may support the design of studies aimed at testing whether restoration of the low T3 syndrome may reduce the high risk of atherosclerotic complications in the CKD population.

In conclusion, serum fT3 levels were inversely associated with CAC scores and measures of arterial stiffness in prevalent PD patients. Both fT3 and CAC scores were also associated with mortality. Specific mechanistic and intervention studies are warranted to clarify the nature of the intriguing link between non-thyroidal illness and vascular calcification.

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