Low-T3 Syndrome in Peritoneal Dialysis: Metabolic Adaptation, Marker of Illness, or Mortality Mediator?

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Thyroid hormone deficiency is a highly prevalent but under-recognized endocrine disorder in patients with CKD, including those on dialysis (1). Among various thyroid hormone deficiency patterns observed in CKD (*e.g.*, subclinical and overt hypothyroidism and low thyroxine [T4]) (1,2), low circulating triiodothyronine [T3] levels (known as the low-T3 syndrome) are the most frequently encountered thyroid functional test derangement in this population (1). For example, in a cross-sectional cohort of 2284 pre-dialysis CKD patients with normal thyrotropin (TSH) levels, there was a graded association between the prevalence of low T3 and incrementally lower eGFR: 8%, 11%, 21%, 61%, and 79% for eGFR levels ≥90, 60 to <90, 30 to <60, 15 to <30, and <15 ml/min per 1.73 m^2, respectively (3). A similarly high prevalence of low T3 has been observed in patients on dialysis (4).

Under the regulation of TSH, the thyroid gland produces two biologically active hormones: T3 and T4 (1). T4 is solely produced by the thyroid, whereas only a small proportion of T3 is secreted from the thyroid gland, with 80% being derived from the deiodination of T4 to T3 in peripheral tissues. The mechanistic link between thyroid functional test derangements and kidney disease is not entirely clear but may be multifactorial and bidirectional. Animal data have shown that thyroid hormone deficiency adversely affects kidney development and structure, manifesting as decreased kidney size to body weight ratio, truncated tubular mass, and glomerular basement membrane changes (1,5). Case reports and case series have also shown that thyroid hormone deficiency results in reduced eGFR, as ascertained by indirect estimating equations and isotopic scans, presumably due to hemodynamic alterations. In a longitudinal study of predialysis CKD patients with mild thyroid hormone deficiency (*i.e.*, subclinical hypothyroidism), exogenous thyroid hormone replacement was associated with a slower decline in eGFR compared with nontreatment (6). Conversely, impaired kidney function may lead to thyroid hormone derangements because of iodine retention through the Wolff–Chaikoff effect (due to exposure from contrast-enhanced imaging studies, fistulograms, angiograms, and povidone-iodine solutions used to sterilize peritoneal dialysis [PD] catheter tips), metabolic acidosis, and selenium deficiency (1). Given that the vast majority of circulating T3 and T4 (>99%) are bound to carrier proteins, it has been hypothesized that patients on PD are at heightened risk for thyroid hormone deficiency resulting from peritoneal effluent protein losses.

Although TSH is the most sensitive and specific single measure of thyroid function given its inverse logarithmic association with T3/T4, circulating T3 has gained recognition as an important metric, because it is the biologically relevant thyroid hormone in end organs such as the heart (7). In fact, the heart is especially vulnerable to the ill effects of low serum T3, because cardiac myocytes are unable to locally generate T3 from its T4 precursor. T3 is not only an important regulator of cardiac-specific genes encoding various structural and functional proteins, it also bears nongenomic actions on cardiac ion channels, organelles, and cytoskeletal components. Consequently, low T3 may potentially lead to a wide range of adverse cardiovascular sequelae, including impaired systolic and diastolic function, increased systemic vascular resistance and hypertension, coronary heart disease, and prolongation of the cardiac action potential and QT interval, leading to ventricular arrhythmias.

However, it is also important to note that the low-T3 syndrome may reflect underlying ill health status. Indeed, low T3 is the hallmark finding of nonthyroidal illness, namely thyroid hormone alterations associated with acute or chronic illness in the absence of thyroid pathology (1). The aforementioned T4 to T3 deiodination process is decreased by various factors that are common in CKD, including inflammation, starvation, certain medications, and high serum cortisol levels. It has, thus, been suggested that low T3 may be a marker of malnutrition, inflammation, and comorbidity burden in patients with CKD.

Given the exceedingly high cardiovascular mortality of CKD patients not wholly explained by traditional risk factors, these data have prompted increasing interest in thyroid hormone deficiency as a risk factor for cardiovascular disease and death in this population (1). Thyroid hormone deficiency was previously thought to be a physiologic adaptation and a means to conserve metabolism in patients with advanced CKD prone to hypercatabolism, dialytic protein and amino acid losses, and protein-energy wasting (8). However, a growing body of evidence suggests that low T3 is associated with decreased systolic function, increased

left ventricular mass, endothelial dysfunction, atherosclerosis, vascular calcification, and altered ventricular conduction in patients on dialysis (Table 1) (9–12). Moreover, some but not all studies have shown that low T3 levels are associated with higher all-cause and cardiovascular mortality in this population (4,13).

In this issue of *CJASN*, Chang *et al.* (14) examined the association between circulating T3 levels and mortality among a prospective cohort of 447 patients who initiated PD over the period of 2000–2007. Thyroid functional tests were measured at baseline as a proxy of long-term exposure–mortality associations. The outcomes of interest were all-cause death as well as several cause–specific mortality end points, including sudden death and combined cardiovascular death. After a median follow-up of 46 months, Chang *et al.* (14) found that a 10-ng/dl higher T3 level was associated with a 14% and a 16% lower risk of all-cause death and combined cardiovascular death, respectively, independent of comorbidities and markers of nutrition and inflammation. Chang *et al.* (14) also observed that a 10-ng/dl higher T3 level was associated with a 31% lower risk of sudden death, and this association was robust in analyses that accounted for competing risks. In contrast to previously published reports, TSH and free T4 levels were not associated with all-cause or cardiovascular death (15,16). However, this study excluded patients whose thyroid functional tests showed overt hypothyroidism (*i.e.*, high TSH and low free T4) or hyperthyroidism (*i.e.*, low TSH) as well as those with known hypo- and hyperthyroidism, which may have restricted the range of observed TSH and free T4 values in this study population (14).

This study provides important contributions to the existing body of literature by (*1*) corroborating that thyroid hormone deficiency may be a novel cardiovascular risk factor in patients with CKD and (*2*) adding incremental knowledge to our understanding of the mechanistic pathways underlying the low T3–mortality association in CKD (14). This is the first study showing an association between low T3 and cardiovascular mortality in patients on PD (14), and it is the first time that the low-T3 syndrome has been shown to predict sudden death in patients with CKD, the leading cause of cardiovascular mortality in this population (1). In addition, by focusing on patients who newly initiated PD, Chang *et al.* (14) were able to detect a crude association between higher T3 level and higher residual kidney function as shown in the baseline characteristics table. Hence, this study adds new insights into thyroid hormone as a potential factor that may influence residual kidney function, a potent predictor of survival in dialysis patients. The study's other noteworthy strengths include its exclusion of prevalent dialysis patients whose characteristics may differ from their incident counterparts; comprehensive consideration of comorbidity, malnutrition, and inflammatory confounders; long follow-up period over which outcomes were tracked; and application of competing risk regression methods to address potential bias associated with traditional Cox regression when analyzing individual causes of death (14).

Several limitations should also be considered when interpreting the study's findings (14). First, given that T3 was measured at a single point in time, analyses did not account for changes in thyroid hormone status over time. To date, only two studies of thyroid function and mortality have examined repeated measures of thyroid functional tests in patients on dialysis (*i.e.*, Meuwese *et al.* [13] examined T3 levels at baseline and 3-month follow-up, and Rhee *et al.* [16] examined time-varying TSH), and additional study of time-varying T3 levels may advance our understanding of the short-term implications of thyroid hormone deficiency in this population. A second limitation is the assumption that circulating T3 levels reflect hormone concentrations at the

Table 1. Selected studies of thyroid hormone deficiency and outcomes in dialysis dependent CKD patients

Study	Cohort (*n*)	Thyroid Metric	Outcome
Cardiovascular surrogates			
Jaroszyński *et al.* (2005) (9)	HD (52)	↓ FT3	↓ Ventricular depolarization
Zoccali *et al.* (2006) (12)	HD + PD (234)	↓ FT3	↓ LV systolic function ↑ LV mass[b]
Tatar *et al.* (2011) (11)	HD (137)	↓ FT3	↑ Atherosclerosis ↑ Arterial stiffness
Meuwese *et al.* (2013) (10)	PD (84)	↓ FT3	↑ Vascular calcification
Mortality			
Zoccali *et al.* (2006) (17)	HD (200)	↓ FT3	↑ All-cause mortality
Ozen *et al.* (2011) (4)	HD (669)	↓ FT3	↑ All-cause mortality[c]
Meuwese *et al.* (2012) (13)	HD (210)	↓TT3 & ↓T4	↑ All-cause and CV mortality
Rhee *et al.* (2013) (15)	HD + PD (2715)	↑ TSH	↑ All-cause mortality
Meuwese *et al.* (2013) (10)	PD (84)	↓ FT3	↑ All-cause mortality
Drechsler *et al.* (2014) (20)	HD (1000)	↓ FT3[a]	↑ All-cause mortality during the first 1 yr of observation
Rhee *et al.* (2015) (16)	HD (8840)	↑ TSH	↑ All-cause mortality

HD, hemodialysis; PD, peritoneal dialysis; FT3, free triiodothyronine; TT3, total triiodothyronine; T4, thyroxine; TSH, thyrotropin; LV, left ventricular; CV, cardiovascular.
[a]Study found no association between subclinical hypothyroidism (↑TSH + ↓FT4) and mortality.
[b]Attenuated to the null after adjustment for IL-6 and serum albumin.
[c]Attenuated to the null after adjustment for high–sensitivity C–reactive protein and serum albumin.

cardiac tissue level; however, a more sensitive and specific metric for intracardiac thyroid hormone signaling has not yet been identified (7). Third, the possibility of residual confounding on the basis of underlying illness cannot fully be excluded. Although multivariable-adjusted analyses took into account several markers of nutrition and inflammation (*e.g.*, normalized protein catabolic rate, lean body mass, albumin, and C-reactive protein), in prior studies of patients with CKD, associations between low T3 and cardiovascular surrogates and/or mortality were abrogated after adjustment for alternative metrics of protein-energy wasting (*e.g.*, IL-6 and high-sensitivity C-reactive protein) (4,17).

Investigating exogenous thyroid hormone replacement in patients with CKD and thyroid hormone deficiency may allow us to better discern the causal implications of the low-T3 syndrome on cardiovascular disease and death. Prior studies of exogenous T3 repletion in patients without CKD and with high cardiovascular risk (*i.e.*, those who have undergone cardiopulmonary bypass surgery) have yielded mixed findings (18). Limited data have shown that, in dialysis patients with low T3 levels, exogenous T3 replacement resulted in greater protein degradation (8). Although thyroid hormone replacement in the form of exogenous T4 (*i.e.*, levothyroxine) is among the most commonly prescribed medication in Medicare Part D enrollees with predialysis CKD and ESRD, its potential risks should be considered (19). Exogenous thyroid hormone replacement may exacerbate protein-energy wasting, one of the strongest predictors of mortality in patients on dialysis, and it could theoretically lead to adverse cardiovascular events (*e.g.*, atrial fibrillation or coronary ischemia) among those in whom treatment is unwarranted. Given their disproportionate prevalence of thyroid hormone deficiency, high burden of cardiovascular disease and death, and frequent use of exogenous thyroid hormone with unclear risks and benefits, rigorous longitudinal studies are warranted to determine how the correction of low T3 and other thyroid functional test derangements affect hard outcomes in the CKD population. Such investigations may allow us to disentangle the low-T3 syndrome's role as a metabolic adaptation, marker of illness, or mediator of mortality in the CKD population.

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Disclosures

None.

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