Thyroid Function and Clinical Outcomes in Kidney Failure

Carmine Zoccali and Francesca Mallamaci


Thyroid hormone synthesis is finely tuned to respond to the variable energy needs of the human body (1). This process is controlled by two fundamental mechanisms. The first, based on the thyroid-stimulating hormone (TSH)–thyroxine (T4) and triiodothyronine (T3) feedback loop, constitutes a sensitive and efficient protection against alterations in thyroid secretion. The second, based on the extrathyroidal generation of T3 from T4, allows rapid adjustments in thyroid hormone availability at tissue level in response to stressful conditions such as nonthyroidal illness. This mechanism is of major relevance because about 80% of the T3 produced results from 5′-deiodination of T4 in peripheral tissues by two T4-5′-deiodinases (type I and type II) (2). Together with the liver, the kidney is the organ endowed with the most abundant deiodinase activity (type 1 4-5′ deiodinase) (2).

Thyroid Hormone Metabolism and the Kidney

Due to reduced deiodinase activity, tissue and circulating levels of the active form of the thyroid hormone, T3, are low in kidney failure (3). Because of reduced renal excretion, inorganic iodide generated by residual deiodinase activity accumulates in stage 4 and 5 CKD, which in turn dampens thyroid hormone synthesis. On the other hand, accumulation of toxic uremic solutes alters the central (hypothalamic) control of the pituitary gland, and the TSH response to thyrotropin-releasing hormone is subnormal in patients with kidney failure (4). In contrast, the thyroid–pituitary feedback loop seems to remain intact, because steady-state plasma TSH remains substantially normal and TSH undergoes the expected rise after thyroidectomy in these patients (5). Central effects apart, toxic uremic solutes such as urea, creatinine, indoles, and phenols inhibit protein binding of T4 (6). Furthermore, studies in the last decade showed that systemic inflammation (7,8) and metabolic acidosis (9) may alter thyroid function in CKD patients.

Low T3 is the most frequent alteration of the thyroid hormone profile observed in CKD. This alteration has long been considered an innocent metabolic adaptation to chronic illness. However, low T3 associates with endothelial dysfunction, a harbinger of atherosclerosis, in stage 3 and 4 CKD patients (10), as well as with cardiomyopathy (11) and with a high risk of death in stage 5D CKD patients (12).

Cardiovascular Disease, Mortality, and Low T3 in Kidney Failure

T3 is a key signal in myocardial cells (13). The causal role of T3 deficiency in heart failure is supported by a short-term clinical trial where synthetic L-T3 replacement therapy elicited a clear-cut improvement in the neurohumoral profile and in left ventricle (LV) performance in these patients (14). Well beyond the heart, T3 should be seen as a critical regulator of cell biology impinging also on cell replication, oxidative phosphorylation, mitochondrial gene transcription, and the generation of various intracellular secondary messengers.

As alluded to before, low T3 in nonthyroidal illnesses, such as kidney failure, was interpreted as a protective adaptation to protein and energy wasting. However, persistently low T3 levels may eventually become a maladaptive response (15), because such an alteration entails a negative prognosis in a variety of severe diseases including diseases treated in intensive care units, liver cirrhosis, pulmonary and cardiac disease, and kidney failure.

Inflammation plays a central role in the high risk of dialysis patients, and inflammation markers have been consistently associated with atherosclerosis, LV dysfunction, and LV hypertrophy in this population. The coherent association of low T3 with high levels of inflammation markers and with mortality and cardiomyopathy suggests that subnormal T3 may be a relevant factor in the chain of events whereby inflammation engenders a high risk for death and cardiovascular disease in this population (12).

Nature of the Link between Thyroid Hormones and Clinical Outcomes

As discussed, low T3 levels (as measured by total or free T3) predict death in dialysis patients and in stage 5 predialysis CKD patients. However, given the observational nature of these findings, the causal nature of this link remains uncertain. Intervention studies are prerequisite for causally implicating any purported risk factor in adverse clinical outcomes, and the randomized clinical trial is at top in the ladder of evidence (16) in clinical research. However, clinical trials are costly and difficult to perform, particularly so in patients with kidney failure. Randomized trials on major clinical problems in this condition are generally made only when biological knowledge gathered in laboratory
experiments and studies at a lower level in the ladder of evidence, namely cohort studies, coherently suggest that it is much more likely that the risk factor being suspected is causally implicated in a particular clinical outcome of interest. For example, the frequent hemodialysis trial was designed and eventually performed only after a robust series of cohort studies coherently indicated that long and/or frequent dialysis may have a favorable impact on the risk of death and cardiomyopathy in this population, a possibility in line with a large series of animal experiments and other sources of biological knowledge.

Among observational cohort studies, a design relating repeated observations of any purported risk factor at the individual level with relevant clinical outcomes is more powerful than one based on a single observation. In this issue of the CJASN, Meuwese et al. (17), for the first time, investigate the link between thyroid hormones and survival by adopting repeated measurements of thyroid hormones. T3, T4, and TSH were measured 3 months apart, and changes during this time interval were related with all-cause and cardiovascular mortality. The risk of death was 2.7 times higher in patients with persistently low T3 compared with those with persistently high levels, and the risk of cardiovascular death associated with persistently low T3 was even greater (hazard ratio = 4.00). Similar trends were found for T4. Thus, the study of Meuwese et al., based on repeated thyroid hormones measurements, substantially confirms findings reported in previous follow-up studies. Such a confirmation should be considered a significant step up in the ladder of evidence in that it provides further circumstantial evidence to the hypothesis that the link between thyroid hormones and clinical outcomes in dialysis patients is causal in nature. The fact that thyroid hormones were measured just twice and after a relatively short time interval and that the data analysis was based exclusively on a categorical approach (high T3 and T4 levels being values in the third tertile and low T3 those in the first tertile) in part reduces the strength of the longitudinal design. As a matter of fact, in patients included in this study, the 33rd percentile of T3 and T4 does not coincide with the lower limit of the normal range in the general population, and many patients in the first tertile had T3 and T4 levels well within the normal range. By the categorical approach, it may happen that a minor change in T3 levels in an individual with T3 levels in the uppermost level of a given tertile moves this individual to the higher tertile and vice versa. Linear modeling is considered preferable to categorical modeling whenever possible. Nonetheless, the categorical approach remains valid in exploratory etiologic studies, such as the present study.

A Clinical Trial in Dialysis Patients with Low T3?

The cogent series of observations in patients with kidney failure and pilot trials of T3 supplementation in other non-thyroidal illnesses, including a short-term trial in patients with heart failure (14), suggest that supplementing T3 may have a favorable influence on clinical outcomes in dialysis patients with low T3. Near physiologic doses of T3 (50 μg/d) produce a negative nitrogen balance in patients with CKD (18), a finding considered as a warning against thyroid hormone supplementation in these patients. However, this may only reflect correction of hypothyroidism, and any increase in protein catabolism can be prevented by adequately augmenting protein intake. Furthermore, the safety of T3 administration in patients with heart failure indicates that it is unlikely that T3 may cause harm to CKD patients with T3 depletion. Metabolic acidosis predicts a high risk of death (19) and is causally associated with low T3 in dialysis patients (9), which may open an interesting and safe perspective for intervention in this population.

In summary, low T3 is a marker of LV hypertrophy and cardiomyopathy and an independent death predictor in follow-up studies in dialysis patients. These observations and the novel study by Meuwese et al. (17), based on repeated measurements of thyroid hormones, lend support to the hypothesis that this alteration is implicated in the high risk of death in this population. These trials are a needed intermediate step to test the causal implication of T3 in major clinical outcome in CKD and will form a more solid basis for a full-fledged randomized clinical trial in this population.

Disclosures

None.

References


Published online ahead of print. Publication date available at www.cjasn.org.

See related article, “Baseline Levels and Trimestral Variation of Triiodothyronine and Thyroxine and Their Association with Mortality in Maintenance Hemodialysis Patients,” on pages 131–138.