

Assessment of Thyroid Disorders and Chronic Kidney Disease: Review Article

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ABSTRACT

Background: The thyroid gland plays a crucial role in human health because it controls several essential physiological processes. Thyroid hormones (T3 and T4) are responsible for a wide range of physiological processes, from metabolism to development to protein synthesis to the regulation of numerous other hormones.

Objective: Review of literature about thyroid disorders as well as chronic kidney disease

Methods: We searched PubMed, Google Scholar, and Science Direct for relevant articles on Thyroid Disorders as well as Chronic Kidney Disease. However, only the most recent or thorough study was taken into account between April 2014 and March 2021. The authors also evaluated the value of resources culled from other works in the same genre. Therefore, documents written in languages other than English have been ignored due to a lack of translation funds. Unpublished works, oral presentations, conference abstracts, and dissertations were generally agreed upon not to qualify as scientific research. **Conclusion:** The impact of thyroid hormone levels on CKD progression is one of the most critical but least well-studied situations. It has been observed that certain amounts of thyroid hormone coexist with disorders in renal function. Fasting, chronic metabolic acidosis, and chronic protein deficiency all contribute to low T3 levels, which may be a marker of chronic kidney disease.

Keywords: Thyroid disorders, chronic kidney disease.

INTRODUCTION

The thyroid gland plays a crucial role in human health because it controls several essential physiological processes. Thyroid hormones (T3 and T4) regulate a wide variety of endocrine systems and play critical roles in metabolic processes, cell growth and differentiation, protein synthesis, and more (Figure 1). Thyroid dysfunction is associated with an array of illnesses because of the hormones it produces (T3 and T4). The impact of thyroid hormone levels on CKD progression is one of the most critical but least well-studied situations. Certain amounts of thyroid hormone have been linked to abnormalities in renal function ⁽¹⁾.

Thyroid disease epidemiology

Thyroid disease affects roughly 7.35% of the population in the United States, or about 1 in 13, or 20 million individuals. The three main types of thyroid disease are underactive, overactive, and subclinical. Overt hypothyroidism affects 0.3% of the US population and subclinical hypothyroidism affects 4.3%, according to the National Health and Nutrition Examination Survey III (NHANES III), the biggest survey of its kind in the US (0.5% have overt hyperthyroidism and 0.75% have subclinical hyperthyroidism). Both hypothyroidism and hyperthyroidism are major causes of morbidity in the United States ⁽²⁾.

Thyroid Physiology:

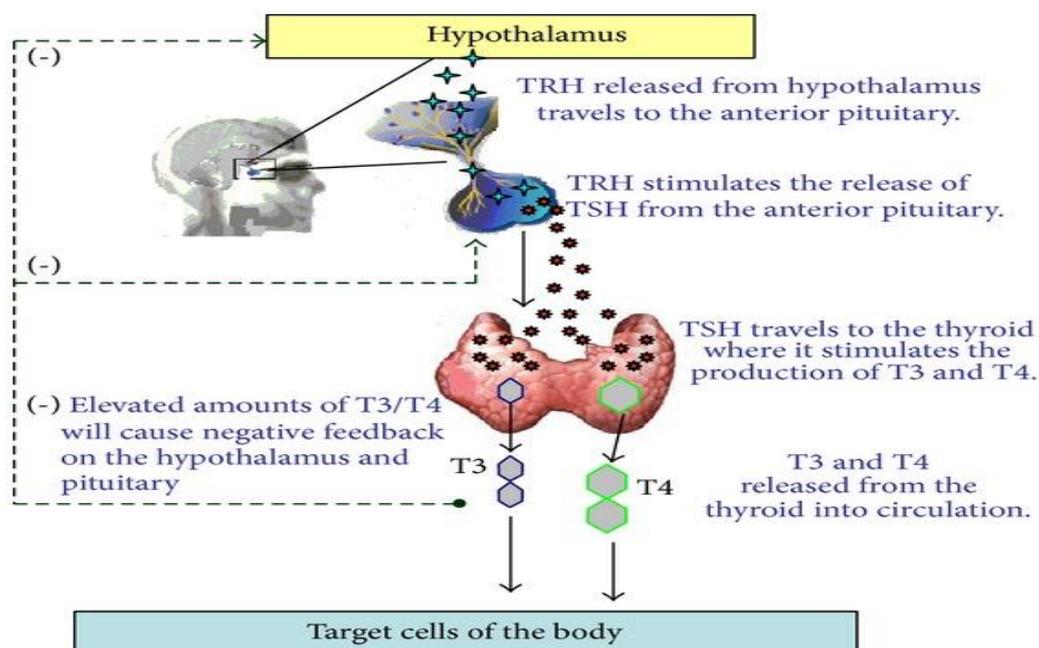


Figure (1): Both T3 and T4 are essential for normal development and adult metabolic homeostasis due to their roles in cell differentiation ⁽³⁾.

Thyrotropin releasing hormone (TRH)

L-pyroglutamyl-L-histidyl-L-prolineamide (L-PHP) is a tiny tripeptide amide that stands in for TRH.

Thyroid hormones in circulation and hypothalamic regulation affect TRH release.

Thyroid stimulating hormone (TSH) is secreted after releasing thyrotropin-releasing hormone (TRH) from the brain and binding to TRH receptors (C-phosphoinositide pathway) (TSH)⁽⁴⁾.

Thyroid stimulating hormone (TSH) (Figure 2):

The thyrotropin hormone (TSH) belongs to the cysteine-knot growth factor super family and has a molecular weight of 28-30 kDa.

The basophilic cells in the anterior pituitary gland are responsible for its production.

When TSH reaches the thyroid gland, it attaches to TSH receptors on the gland's cells.

TSH is secreted by the anterior pituitary. This physiological process initiates thyroid gene expression and T3/T4 synthesis ⁽⁵⁾.

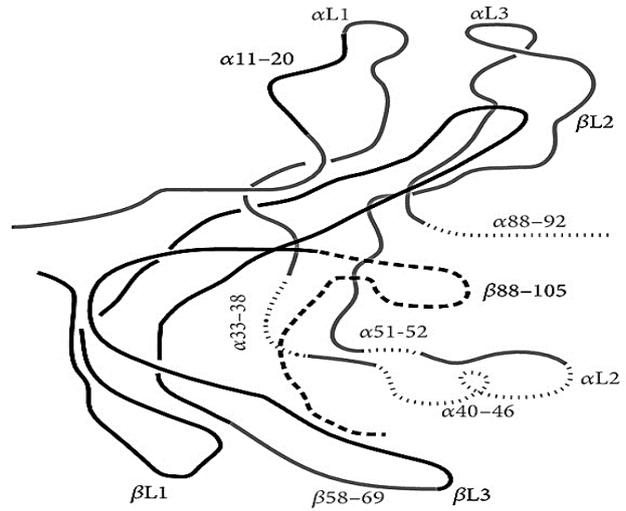


Figure (2): The Thyrotropin hormone structure⁽³⁾.

Chromosomes 1 and 6 contain the human and components for the thyrotropin hormone. The alpha subunit gene (which has 5 exons and 3 introns) is roughly twice as large as the subunit gene. The effector region, or alpha subunit, is responsible for stimulating the second messenger pathways. The physiological role of the subunit is crucial to thyrotropin receptor selectivity ⁽⁵⁾.

Chronic kidney disease and thyroid conditions (Figure 3):

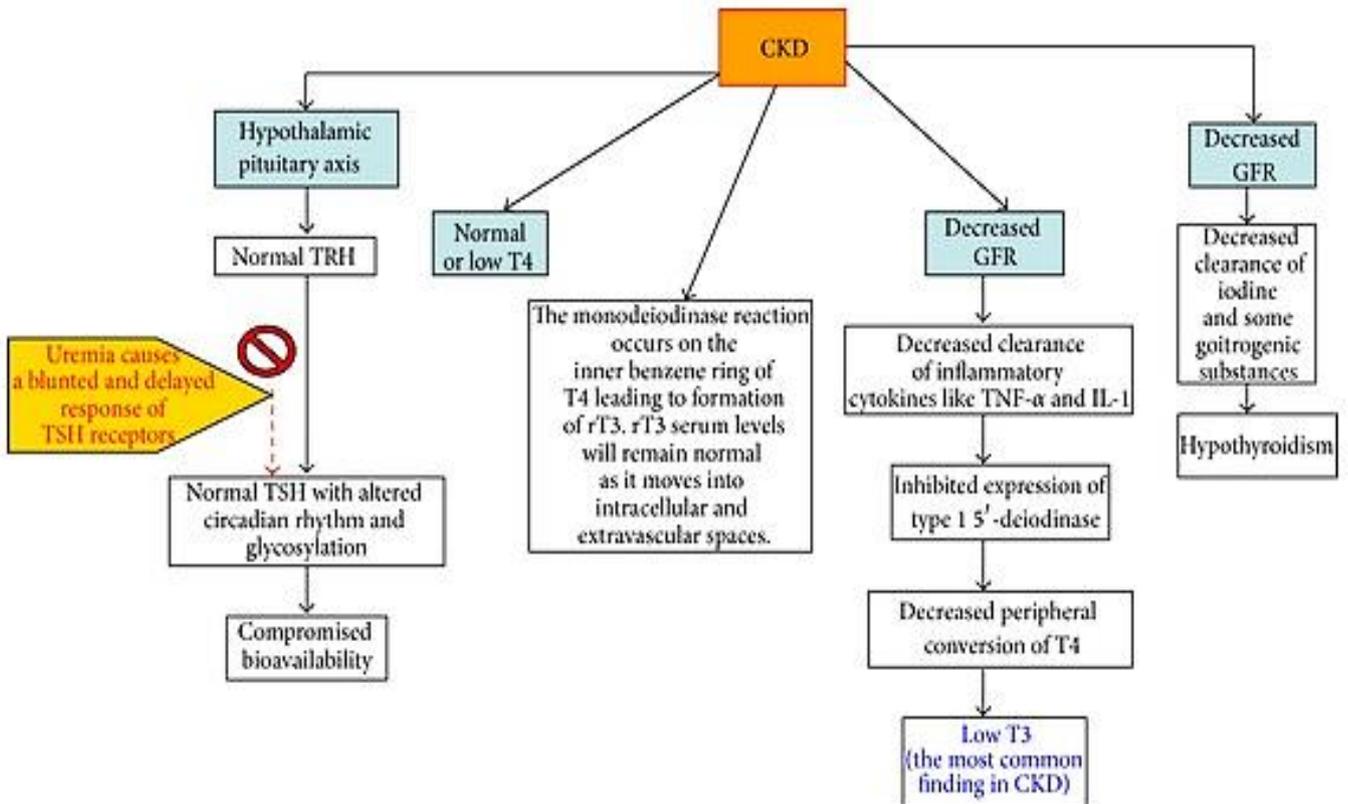


Figure (3): Chronic kidney disease and thyroid conditions ⁽³⁾.

Both central and peripheral thyroid hormone metabolism are affected by chronic kidney disease. Subclinical hypothyroidism, characterized by low T3, is the most frequent thyroid issue in people with chronic kidney disease. Changes in the circadian rhythm typically accompany normal TSH levels (comprised of TSH bioactivity). Reduced TSH release occurs as a result of a decreased response of pituitary receptors to TRH, which occurs in uremia. TSH's reaction to TRH is slowed because its clearance is reduced and its half-life is lengthened ⁽⁶⁾. T3 and T4 can be displaced from normal protein binding sites by abnormal serum components, which are present in uremic situations. The creation of reverse T3 from monodeiodinase action on T4's inner benzene ring rather than its outer ring may account for normal or low T4 levels. Patients with CKD have normal levels of reverse T3.

However, since the hormone diffuses out of blood vessels and into extravascular and intracellular regions. After undergoing hemodialysis, a transient elevation in T4 levels is common. The anticoagulant heparin is responsible for this action because it prevents T4 from attaching to proteins, which raises T4 concentrations ⁽⁷⁾.

Fasting, chronic metabolic acidosis, and chronic protein deficiency are all characteristics of CKD and may contribute to low T3 levels in this disease. The proteins that bind to T3 can be affected by such variables. Low T3 levels in CKD may also result from impaired clearance of inflammatory cytokines including TNF-alpha and IL-1.

The overall amount of T3 produced by the body, outside of the thyroid, would subsequently decrease. These cytokines inhibit 1 5'-deiodinase, an enzyme required for T4 to T3 conversion. Patients on hemodialysis have been found to have an increased risk of death if their free T3 levels are low ⁽⁸⁾. Graft loss after renal transplantation is more likely when T3 levels are

low beforehand. T3 levels should be checked prior to performing a kidney transplant on any patient. In CKD, low T3 levels may prevent TSH from rising.

There is some evidence from experiments to show that thyrotrophs become more sensitive in uremia. This may explain why the negative feedback inhibition is changed once the central thyrostat is reset, indicating a decrease in circulating thyroid hormones ⁽⁹⁾.

Goiter in CKD:

Goiter is more common in CKD patients, with a prevalence ranging from 0 to 9%. Hypertrophy of thyroid gland tissue leading to goitre may result from reduced elimination of inorganic iodides. It is possible that chronic kidney disease contributes to a decrease in the clearance of goitrogenic compounds such as aryl acid. The Wolff-Chaikoff effect has been demonstrated to be prolonged by elevated serum iodine levels ⁽¹⁰⁾.

Subclinical Hypothyroidism:

An increased blood TSH concentration and a normal serum free T4 concentration characterise subclinical hypothyroidism. Subclinical hypothyroidism prevalence steadily rises as GFR declines. Subclinical primary hypothyroidism was found in about 18% of patients with CKD who did not need dialysis. This observation is unrelated to the predicted GFR being lower.

Subclinical primary hypothyroidism was shown to be more common in people whose GFR fell from 90 mL/min to 60 mL/min, from 7% to 17.9%. Reduced requirement for hormone replacement therapy due to correction of hypothyroidism caused by reduction of dietary iodine in uremic patients on dialysis has been reported by certain researchers. In one clinical experiment, those who were not given thyroid hormones experienced a much faster reduction in estimated GFR compared to those who were ⁽¹¹⁾.

Hyperthyroidism (Figure 4):

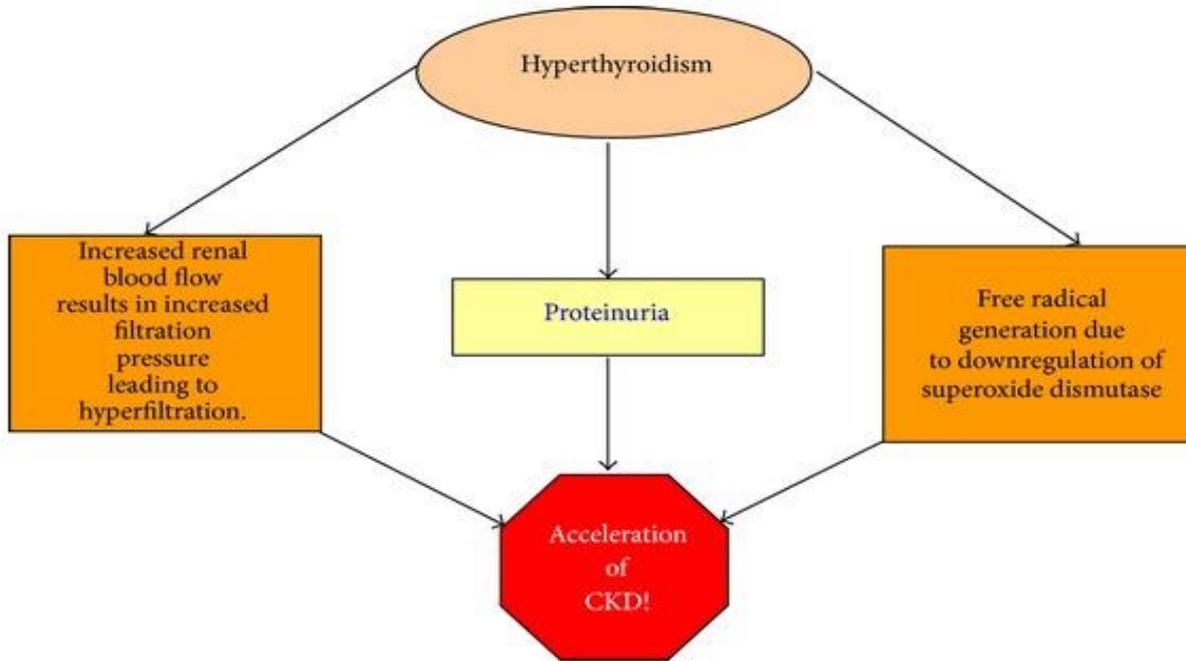


Figure (4): Hyperthyroidism and chronic kidney disease ⁽³⁾.

CKD is not directly linked to hyperthyroidism, as its prevalence is similar to that of the general population. Some elements of hyperthyroidism, however, have been shown to hasten the progression of chronic kidney disease. The following are examples of such mechanisms ⁽³⁾:

- i. Hyperthyroidism causes hyperfiltration due to increased filtration pressure and intraglomerular hypertension due to increased renal blood flow. Direct renal injury can be brought on by the proteinuria associated with hyperthyroidism;
- ii. Hyperthyroidism induces kidney damage due to increased free radical production from increased mitochondrial energy consumption and downregulation of superoxide dismutase;
- iii. Hypertension in hyperthyroidism is a risk factor for chronic kidney disease and is exacerbated by oxidative stress ⁽³⁾.

Thyroid Disorders in Glomerular Diseases

Several forms of glomerulonephritis have been linked to thyroid conditions like hypothyroidism and hyperthyroidism and minimal change glomerulonephritis are the most common forms of glomerulonephritis in patients with thyroid illness. Most common is a condition called membranous glomerulonephritis. Immune complex deposition causes a thickening of the glomerular basement membrane (GBM), and an increase in mesangial and endocapillary cellularity are the two most prominent histological alterations ⁽¹²⁾.

Thyroid dysfunction is associated with glomerulonephritis through a pathogenesis that involves

proteinuria and the production of immune complexes. Autoimmune thyroiditis is characterised by this correlation almost always. Immune complexes are present in up to half of patients with autoimmune thyroiditis. These complexes, which deposit on the glomerular basement membrane, are largely responsible for the modification of renal function. There has been evidence that thyroglobulin accumulates in the glomerular basement membrane. Parallels can be drawn between thyroid disease and other autoimmune conditions, such as systemic lupus erythematosus (SLE) as well as diabetes ⁽¹³⁾.

Nephrotic Syndrome

Thyroid hormone levels in the blood can have a number of consequences for nephrotic syndrome. Proteinuria results in the loss of many binding proteins, including thyroxine-binding globulin (TBG), transthyretin or prealbumin, and albumin. When these proteins are lost, serum T4 and total T3 levels drop below normal. The vast majority of people who have proteinuria are euthyroid, meaning their thyroids produce an adequate amount of free T3 and T4. Substituting levothyroxine for thyroid hormones has not been settled ⁽¹⁴⁾.

Thyroid cancer and kidney disease

Thyroid cancer is becoming more common everywhere. Thyroid cancer strikes 3 times as many women as men. Thyroid cancer patients are at increased risk for developing other cancers, including renal cell carcinoma. Thyroid hormones and reproductive malignancies have been the subject of numerous

investigations. Renal sarcoma, oncocytoma, collecting duct tumours, and parenchymal epithelial tumours are some of the others. Metastasis from papillary thyroid carcinomas can spread to the kidneys' follicular⁽³⁾.

Effects of dialysis on thyroid hormones hemodialysis

Hemodialysis (HD) patients typically have normal thyroid function. Low T3 levels are linked to systemic acidosis, dialysis duration, endothelial damage indicators, and inflammation caused by HD. Total T4 levels are decreased and free T4 levels are increased in these patients because heparin blocks T4 binding to proteins. Thyroid stimulating hormone (TSH) elevations occur in 20% of HD patients, typically in the 5-20 mU/L range. One possible compensatory mechanism for euthyroid state in HD is altered TSH cellular transport⁽¹³⁾.

Peritoneal Dialysis

Subclinical hypothyroidism and low T3 levels are common in people who undergo peritoneal dialysis (PD). As there is a correlation between free T3, CRP, and serum albumin. Low T3 levels in PD may be the result of inflammation and malnutrition. Reduced iodide clearance may play a role in the development of subclinical hypothyroidism. Since glomerular filtration is responsible for the majority of iodide clearance, the excretion of iodide is reduced in advanced CKD, leading to an increase in plasma inorganic iodide concentration. High rates of subclinical hypothyroidism among CKD patients have been linked to elevated levels of inorganic iodide in the body. Small (10%) and readily compensated (1% in PD), T4 and T3 losses are to be expected. Patients on PD do not require thyroid hormone supplements⁽¹⁵⁾.

Although TBG is lost along with T4 and T3 in the PD, levels are normal despite this. Recent research indicates that people with CKD who also suffer from subclinical hypothyroidism are at an increased risk for cardiovascular disease and mortality⁽³⁾.

Renal Transplant

Thyroid hormone levels are reported to return to normal after a kidney donation. In kidney transplant patients, low T3 and T4 gradually return to normal within 3 to 4 months. T4 levels are decreased less drastically than in the pre-transplant stage and progressively return to normal throughout the first several months after a transplant. Graft function in post-transplant patients is typically correlated with free T3 and thyroid volume. Treatment with thyroid medications is unnecessary for individuals with low pre-transplant T3 levels because doing so increases the chance of graft loss⁽¹⁶⁾.

Prevalence of hypothyroidism in CKD

Little is known about the prevalence or severity of thyroid abnormalities in ESRD patients, despite the fact that the symptoms of hypothyroidism (such as fatigue, lethargy, cognitive, and sexual dysfunction) are highly

overlapping with those of severe CRF. Higher rates of goitre and bigger thyroid glands have been seen in patients with ESRD. Hypothyroidism has been linked to an increased risk of death in ESRD patients. Low levels of thyroid hormones (TT3, FT3, and TT4) as well as FT3 and FT4 suppression have been linked to ESRD. It is unknown what causes these alterations, but they may represent a compensatory response to persistent non-thyroidal disease, unresolved uremia, and protein deficiency⁽¹⁷⁾.

Due to decreased urine iodine excretion in CRF, blood inorganic iodine levels and thyroid iodine content rise, leading to enlargement of the gland. Dialysis patients are more likely to develop goiters due to increased povidone-iodine absorption through the skin. Previous studies found a wide range in the prevalence of hypothyroidism among hemodialysis (HD) patients. Twenty-one percent of HD patients were found to have subclinical hypothyroidism, while only 7.14% of the control group did⁽¹⁸⁾.

According to **Pakfetrat et al.**⁽¹⁷⁾ hypothyroidism in ESRD patients may not present clinically due to factors like uremia, malnutrition, and other illnesses. Patients with HD are more likely to experience thyroid hormone abnormalities, nodular goitre, and hypothyroidism than the general population. Hypothyroidism was linked to an increased risk of death in ESRD patients, however treatment with thyroid hormone may mitigate this link⁽¹⁷⁾.

Studies using ultrasonography have indicated a higher incidence of goitre and thyroid gland volume in ESRD patients who are receiving HD. Wolff-Chaikoff effect, in which increased total body inorganic iodine inhibits thyroid hormone synthesis, may account for the increased incidence of goitre in these patients. Furthermore, some scientists have hypothesized that increased TSH levels may contribute to the increased prevalence of goiter⁽¹⁹⁾.

The majority of participants in the control group (86%) had normal levels of TSH, T3, and FT4 compared to just 63% of participants in the ESRD group in the study by **Da Costa et al.**⁽²⁰⁾. Patients with low T3 are more likely to be in later stages of chronic kidney disease, as shown by **Song et al.**⁽²¹⁾. However, they suggested measuring T3 levels even in the beginning stages of CKD because of the clear association between this hormone and GFR. Subclinical hypothyroidism affects between 4 and 10% of the population at large and between 7 and 26% of the elderly⁽¹¹⁾. The frequency of subclinical hypothyroidism was higher in the ESRD cohort than in the control group (21.82% vs. 7.14%, $P = 0.03$). According to a study by **Da Costa et al.**⁽²⁰⁾ GFR has been associated to both overt and covert hypothyroidism. Thyroid disturbance has been linked to advanced chronic kidney disease, although the underlying mechanism is unclear. Iodine metabolism changes, diminished peripheral sensitivity to hormones, and autoimmune thyroiditis are just few of the potential explanations⁽¹¹⁾.

Decompensation in T3 input and outflow during dialysis that would preserve euthyroid condition may account for the presence of subclinical hypothyroidism in uremic patients, a phenomenon shared by many chronic diseases. Inhibition of protein binding to T4 by heparin prior to dialysis increases the free fraction of T4, which in turn reduces the negative feedback that causes an increase in TSH release ⁽²²⁾.

CONCLUSION

The impact of thyroid hormone levels on CKD progression is one of the most critical but least well-studied situations. It has been observed that certain amounts of thyroid hormone coexist with disorders in renal function. Fasting, chronic metabolic acidosis, and chronic protein deficiency all contribute to low T3 levels, which may be a marker of chronic kidney disease.

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