Retrospective comparison of thyroid hormone levels in early and late stages of chronic kidney disease

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RETROSPECTIVE COMPARISON OF THYROID HORMONE LEVELS IN EARLY AND LATE STAGES OF CHRONIC KIDNEY DISEASE

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LIST OF ABRREVIATIONS

ACE – angiotensin converting enzyme

ANOVA – analysis of variance

Ca2+ – calcium

CI – confidence interval

CKD – chronic kidney disease

CKD-MBD – chronic kidney disease-mineral bone disorder

CNS – central nervous system

CRP – c-reactive protein

CSF – cerebrospinal fluid

DIO1 – deiodinase type 1

DIO2 – deiodinase type 2

DIO3 – deiodinase type 3

ESRD – end stage renal disease

ESS – euthyroid sick syndrome

FGF23 – fibroblast growth factor-23

fT3 – free triiodothyronine

fT4 – free thyroxine

GFR – glomerular filtration rate

HAS – human serum albumin

HPT axis – hypothalamic-pituitary-thyroid axis

ICD – international statistical classification of diseases and related health problems

ICU – intensive care unit

IL-1 – interleukin 1

IRCT – interventional randomized controlled trial

IQR – interquartile range

K+ – potassium

KDIGO – kidney disease: improving global outcomes

L-T4 – Levothyroxine

MCT8 – monocarboxylate transporter 8

NTIS – non-thyroidal illness syndrome

Na+/K+ ATPase – sodium potassium adenosinetriphosphatase

Na+ – sodium

PI3K/AKT – phosphatidylinositol 3-kinase or serine/threonine-protein kinase

PLN – phospholamban

PTH – parathyroid hormone

PVN – paraventricular nucleus

RBF – renal blood flow

rT3 – reverse triiodothyronine

SERCA2 – sarcoplasmatic/endoplasmatic reticulum calcium ATPase 2

SCr – serum creatinine

TBG – thyroxine-binding globulin

TNF-α – tumor necrosis factor α

TPO – Thyroid peroxidase

TRH – thyrotropin-releasing hormone

TREs – thyroid hormone response elements

TSH – thyroid-stimulating hormone

TH – thyroid hormone

TTR – transthyretin

UCP-1 – uncoupling protein-1

1. INTRODUCTION

The global prevalence of chronic kidney disease (CKD) is increasingly rising, currently affecting approximately 850 million people. It is now the seventh most significant risk factor for mortality. Projections indicate that by 2040, CKD will rise to be the fifth leading cause of death among non-communicable diseases (1,2).

Patients diagnosed with CKD and end-stage renal disease (ESRD) often have prevalent additional thyroid dysfunctions. They manifest as hypothyroidism or subclinical hypothyroidism and nonthyroidal illness syndrome (NTIS) also known as, euthyroid sick syndrome (ESS) and low T3 syndrome (3,4).

Complications related to CKD such as metabolic acidosis, uremia, chronic inflammation and hypoalbuminemia alter thyroid hormone (TH) activity on peripheral level. Several mechanisms can lead to this finding, including abnormal bindings to carrier proteins, decreased TH in tissues and reduced iodine clearance with its consequent retention in the thyroid gland. Thus, levels of both triiodothyronine (T3) and thyroxine (T4) can be diminished, however, without an increase in thyroid stimulating hormone (TSH) response. The reduction of T3 is attributed to impaired enzymatic activity of deiodinase, consequently decreasing extrathyroidal conversion of T4 to T3. On the other hand, T4 is likely lowered by its impaired binding to thyroxine-binding globulin (TBG) due to circulating inhibitors (5,6).

Epidemiologic data indicate increased morbidity among CKD patients concurrently affected by NTIS, proposing that low free triiodothyronine (fT3) levels are associated with higher mortality rates compared to those with normal fT3 levels. The correlation is especially significant because both low TH levels and CKD can promote major cardiovascular events, leading to higher risk of death (7).

While some research suggests a protective role of decreased thyroid state against muscle wasting and high energy expenditure in critical illness, others propose that early TH substitution in patients with CKD may have a beneficial outcome for disease progression and mortality. Considering the conflicting data, further research is necessary to examine the impact of low fT3 levels on the progression of kidney disease and to evaluate the prognostic role of TH substitution therapy (6,8).

This study aimed to investigate impaired peripheral conversion of free thyroxine (fT4) to fT3 across stages two and four of CKD, with a particular focus on finding higher prevalence of low fT3 levels associated with increased severity of CKD. Additionally, the impact of thyroid hormone supplementation on thyroid parameters was compared between CKD groups.

1.1 The Thyroid Gland

The thyroid gland is an endocrine organ, involved in hormone productions responsible for the regulation of growth, metabolism and serum electrolyte concentrations. Within the thyroid follicle, around 10% of the more potent TH is produced, or T3, while 90% of TH production constitutes T4, which will be converted to T3 peripherally (9,10).

1.1.1 Anatomy

The anatomic position of the thyroid gland is in the anterior neck, anterior to the trachea. It consists of two lobes which are connected in the midline by the isthmus. The gland receives its high vascularization from the superior and inferior thyroid arteries and venous drainage by the superior, middle and inferior thyroid veins. Lymphatic drainage occurs along the prelaryngeal, deep cervical, pretracheal, and paratracheal nodes. The nerve innervation of the thyroid is linked to its vascular supply rather than its endocrine function, involving parasympathetic fibers from the vagus nerve and sympathetic fibers from the superior, middle and inferior ganglia of the sympathetic trunk (11).

The functional unit of the thyroid gland are the thyroid follicles made up of cuboidal cells and follicular cells. Within the latter TH are being produced and secreted. Located on the walls of the thyroid follicles are the parafollicular cells, also known as C cells, that secrete calcitonin. Furthermore, the follicles store the colloid which beholds the large protein thyroglobulin (12).

1.1.2 Physiology

1.1.2.1 Hypothalamic-Pituitary-Thyroid Axis

TH release is controlled through the hypothalamic-pituitary-thyroid (HPT) axis which is a self-regulatory circuit. Initially, the hypothalamic secretion of thyrotropin-releasing hormone (TRH) stimulates the anterior pituitary gland for synthesis and excretion of TSH. TSH in turn signals the production and secretion of thyroid hormones T3 and T4 from the thyroid gland. To maintain homeostasis, TH act on the hypothalamus and anterior hypophysis through a negative feedback mechanism (13,14).

Downregulation of the HPT axis may represent a physiologic adaptation in CKD with initial protective function, potentially aimed to reduce metabolic demand during illness. Complications such as uremia are often associated with low-grade chronic systemic inflammation characterized by elevated levels of pro-inflammatory cytokines. These cytokines, such as interleukin 1 (IL-1), can in turn, suppress the release of hormones from the hypothalamus and pituitary gland and additionally disrupt the peripheral conversion of fT4 to

fT3, contributing to the development of low T3 syndrome. With progressive renal dysfunction, TH abnormalities arise. Approximately 14% of patients exhibit elevated TSH levels, irrespective of their fT4 concentrations, while more than 75% of individuals show a decrease in fT3 (15,16).

1.1.2.2 Thyroid Hormone Synthesis

The synthesis of thyroid hormones involves five key steps. Initially, the precursor protein, thyroglobulin is produced within the thyroid follicular cells. Secondly, iodide uptake by thyrocytes is initiated via protein kinase A which stimulates the active transport of the basolateral Na+/I- symporters. Once iodide diffuses towards the cell apex, it is transported into the colloid by the pendrin transporter. The following step involves the iodination of thyroglobulin through a cascade of biochemical reactions. Protein kinase A activates thyroid peroxidase (TPO) through phosphorylation. TPO serves three distinct functions in the process of iodinating thyroglobulin. In the first reaction, TPO oxidizes iodide (I-) to iodine (I2), using hydrogen peroxide (H2O2). Next, organification takes place wherein TPO attaches I2 to the tyrosine residues of thyroglobulin, yielding monoiodotyrosine (MIT) and diiodotyrosine (DIT). Finally, TPO catalyzes the coupling of one or two tyrosine molecules to MIT and DIT, producing triiodothyronine (T3) and tetraiodothyronine (T4). The resulting thyroid hormones are then stored in the lumen of the follicle. To release the TH, endosomes containing iodinated thyroglobulin fuse with lysosomes, leading to enzymatic cleavage into MIT, DIT, T3 and T4. Monocarboxylate transporter 8 (MCT8) subsequently delivers T3 and T4 into the capillaries while deiodinase enzyme recycles iodine from thyroglobulin for the next synthesis (9,14,17).

1.1.2.3 Role of Peripheral Deiodinases

Deiodinases are selenium cysteine containing enzymes involved in the activation and deactivation of TH. There are three primary types of deiodinases, type 1 (DIO1), type 2 (DIO2) and type 3 (DIO3) which are expressed in various tissues and yield different catalytic properties (18,19).

DIO1 is mostly found in the kidneys, liver and thyroid gland. It catalyzes the conversion of T4 to T3 and reverse T3 (rT3), an inactive form of the hormone that additionally plays an important role in recycling iodine. In contrast, DIO2 is present in the central nervous system (CNS) and is responsible for converting more than 75% T3 from T4 within the brain. This process in turn is crucial for the regulation of the negative feedback system involved in the homeostasis of TH levels. An increase in T3 in the CNS leads to the inhibition of TRH synthesis by neurons in the hypothalamic paraventricular nucleus (PVN) and thus an inhibition of TSH secretion. Whilst

DIO1 and 2 are responsible for the peripheral activation of T3, the third deiodinase (DIO3) has opposing qualities. It terminates the action of T3 and T4 by initiating inner ring deiodination (18,20–23)**.**

CKD causes multiple alterations in the activity of deiodinase enzymes. Chronic metabolic acidosis and NTIS reduce the deiodinase activity. Furthermore, initiation of tumor necrosis factor α (TNF-α) and interleukin 1 (IL-1) during inflammation inhibit the expression of deiodinase type 1 and 2, resulting in depressed levels of T4 to T3 conversion. However, rT3 levels in non-thyroidal illness may be elevated due to reduced turnover and increased synthesis (5).

The study conducted by Niemczyk et al. highlights the clinical significance of both cortical and medullary DIO1 and DIO2 enzymes in renal disease, underscoring their potential involvement in thyroid hormone metabolism (24).

1.1.2.4 Circulatory Transport

The hydrophobic nature of TH requires binding proteins for its proper distribution throughout the body. Thus, T4 and T3 are almost entirely bound to carrier proteins including thyroid binding globulin (TGB), transthyretin (TTR), and huma serum albumin (HSA) with only less than 1% of free circulating hormone available to act on target tissues. Amongst those transporters, TGB carries approximately 75% of T4 and T3 due to its high affinity, followed by TTR with 15-20% bound T4 and 5% bound T3 in serum. The remainder is attached to HAS with less than 5% of T4 and less than 20% of T3. Although HAS transports less TH in comparison to TGB and TTR, it being the most abundant plasma protein, denotes its significance in contributing to the total pool of TH. Furthermore, TGB acts as a serpin and is crucial for the maintenance of a stable TH level. TTR on the other hand is the major carrier protein for delivery of TH to the brain, thus found within the cerebrospinal fluid (CSF). During uremia, the binding of T4 and T3 to serum carrier proteins is impaired. Besides the transporting effects of thyroid hormone-binding proteins, they additionally lower iodide loss. The crucial transporter MCT8 imports TH into the cell. Within the cell, TH acts by binding to thyroid hormone receptors, included in the nuclear receptor superfamily. Those receptors in turn attach to particular thyroid hormone-responsive sequences in promoters of target genes and hence influence transcription. Uremia is suggested to inhibit the uptake of T4 into the hepatocytes, thereby preventing DIO1 from converting T4 to T3 (5,15,21,25–29).

1.1.2.5 Target Tissue Action

TH impacts nearly all nucleated cells of the body, influencing normal development, growth, metabolism and neuronal differentiation (9,30).

On the heart, TH exudes positive chronotropic and inotropic effects, increasing cardiac output, stroke volume and resting heart rate. These responses are accomplished via genomic and non-genomic pathways. Among the genomic response, T3 adheres to the nuclear thyroid hormone receptor of the cardiomyocyte, further binding to thyroid hormone response elements (TREs) and ultimately influencing promoters of target genes. Modulation of cardiac contractility and ejection fraction is generated by upregulation of Na+/K+ ATPase, alpha-myosin heavy chain and SERCA2 and downregulation of beta-myosin heavy chain and phospholamban (PLN). The exertion of non-genomic effects of TH includes affecting membrane ion channels (Na+, K+, Ca2+) and initiation of PI3K/AKT signaling, thus counteracting apoptosis in vascular smooth muscle (9,26,31,32).

Thyroid function regulates basal metabolic rate (BMR) and heat production through enhancing thermogenesis and increasing oxygen consumption. Adaptation upon cold exposure is mediated via induction of DIO2, locally elevating T3 conversion in brown adipose tissue (BAT), thus upregulating uncoupling protein-1 (UCP1-1), also known as thermogenin. Corresponding to the metabolic needs, TH either initiate lipolysis or lipid synthesis. Furthermore, it stimulates carbohydrate reabsorption, gluconeogenesis, glycogen synthesis and glucose oxidation. While TH exhibits anabolic effects on proteins, at high levels, it induces protein catabolism (9,33–35).

Kidney physiology is influenced through pre-renal and direct renal effects of TH. Stimulation of nitric oxide synthase (NOS) in the renal cortex and medulla leads to an accumulation of nitric oxide (NO), causing endothelial vasodilation. This process, accompanied by a decrease of renal vasoconstriction via endothelin, increases renal blood flow (RBF). Thereby the direct effects present themselves by an increased glomerular filtration rate (GFR), tubular secretion and reabsorption. TH elevates beta-adrenergic activity and upregulates the number of beta-adrenergic receptors in the renal cortex. Additionally, T3 stimulates renin gene expression which increases levels of angiotensin II and angiotensin converting enzyme (ACE). These effects induce the renin-angiotensin-aldosterone system (RAAS), further elevating GFR. (1)

Apart from said effects, the thyroid encompasses multiple other functions: Increased oxygenation through elevated respiratory rate, minute ventilation and increased oxygen delivery due to erythropoietin (EPO) stimulation. Additionally, it increases uptake of folate and

Vitamin B12 from the gastrointestinal tract. Stimulation of bone growth, regulation of ovulatory cycle and spermatogenesis, enhancement of renal blood flow and glomerular filtration rate are further manifestations (9,14).

1.2 Non-thyroidal illness syndrome (NTIS)

Non-thyroidal illness syndrome, also known as euthyroid sick syndrome (ESS) and low-T3 syndrome is encountered in severe illness or starvation. Its hallmarks are decreased levels of fT3 and/or fT4 without subsequent increase of TSH but with an increase in rT3(8,19,29,36–38).

New evidence suggests NTIS resulting from a complex interplay between central hypothyroidism and altered peripheral conversion of T4 to T3, leading to a decreased serum and tissue thyroid hormone concentration. Hence, underlying sicknesses, including kidney diseases, inflammatory conditions, myocardial infarction, major surgery, trauma and starvation are major catalyzers for the development of NTIS (29,39).

Compared to real hypothyroidism, NTIS is rather discussed as an adaptive mechanism. By decreasing TH, the BMR, protein catabolism and caloric expenditure is lowered, thus reducing the overall demand in critical illness and starvation. With disease progression, a gradual drop in T4 levels arises in addition to the reduced T3 concentration (29,40,41).

The morbidity of NTIS in patients with CKD is rising with NTIS having a larger influence on the short-term prognosis rather than the long-term prognosis (8).

1.2.1 Pathogenesis

Several mechanisms contribute to the pathogenesis of non-thyroidal illness syndrome amongst which inflammation is the is a major influence. Extensive studies have proven that inflammatory mediators such as cytokines and signal transduction pathways are involved. Interleukin 6 (IL-6) may have negative correlations with serum T3 in hospitalized patients. In the context of CKD, proinflammatory states characterized by increased levels of IL-6 and TNF-α emerge. Elevation of IL-6 and TNF-α levels oftentimes precede a decrease in serum T3 and T4 seen in NTIS. Moreover, the subunit RelA within the nuclear factor kB (NF-kb) pathway enhances DIO2 activity upon activation, elevating T3 levels in the CNS. This increase in T3 initiates a negative feedback loop, ultimately leading to a decrease of overall TH production (7,19,23). In comparison, DIO1 activity is downregulated, affecting the conversion of active TH (42). Additionally, the adherence of TH to thyroid-binding protein may be hindered by thyroid-binding hormone inhibitors, distributed throughout the tissues of the body and serum, thus inhibiting the action of T3 on a cellular level (29,42).

Albumin is responsible for the translocation of TH from its carrier protein TGB by binding to fatty acids. With the fall of serum albumin concentrations in patients with euthyroid sick syndrome, the binding to TBG by competitors of T4 is favored (42).

Suppressed TRH secretion, decreased conversion of T3 to T4, reduced production of T3 in the liver, raised rT3 synthesis and a down-regulation of deiodinases, transporters and thyroid hormone receptors are further mechanisms leading to NTIS (29).

In conclusion, the pro-inflammatory state of CKD potentiates the development of NTIS, creating a self-perpetuating cycle (40).

1.2.2 Clinical Significance

Based on a meta-analysis performed in 2019, a rise of morbidity by nearly 79% in NTIS patients with chronic renal failure (CRF) was seen. The analysis revealed a rather short-term implication of mortality related to NTIS, with continuous decrease in the follow-up years (8).

Furthermore, a prospective observational study performed in India revealed a significant association between NTIS, particularly low levels of T3 and fT3, and an increased mortality in sepsis patients. The findings therefore highlight the importance of monitoring TH levels as a potential indicator of prognosis in critical illness such as sepsis (43).

Another study conducted in Leipzig Germany, found a positive association between NTIS and several adverse outcomes, including prolonged ICU and hospital stays, increased need for mechanical ventilation, higher incidence of sepsis, acute respiratory distress syndrome (ARDS), acute liver failure, acute kidney injury (AKI) and increased ICU mortality. However, NTIS was not found to be an independent predictor for increased ICU mortality. Instead, the duration of mechanical ventilation, along with the occurrence of AKI, sepsis and acute liver failure, were identified as independent predictors of mortality (44).

1.2.3 Differential Diagnosis

Distinguishing between severe primary hypothyroidism and NTIS can be challenging. However, the lack of concomitant increase of TSH alongside decreased fT3 and fT4 levels is indicative for NTIS (45). The presence of positive anti-TPO antibody titers supports the diagnosis of primary hypothyroidism. Additionally, low thyroid hormone-binding ratio, low serum rT3 levels and high ratio of fT3 to fT4 support the existence of hypothyroidism compared to NTIS. Critically ill patients with simultaneous hypothyroidism that take medications such as dopamine may experience inhibited TSH release, while anticonvulsants and glucocorticoids can decrease fT4 levels, thus further complicating the differentiation (19,46).

1.2.4 Treatment and Management

Treatment for patients with NTIS with TH substitution is still debated. It is evident that the mortality rate for ICU patients with NTIS can reach up to 70%. However, studies so far have not provided conclusive results. Sciacchitano et al.'s meta-analysis of interventional randomized clinical trials (IRCTs) for TH therapy underscores this uncertainty. Furthermore, Fliers et al. reviewed clinical outcomes for TH treatment in severe illness, finding mostly non-beneficial results. There may be exceptions for patients with heart failure, who have profited from TH supplementation. Similarly, an IRCT performed by Liu et. al., demonstrated that TH replacement therapy in patients with nephrotic syndrome allowed for regression of ESS without any apparent side effects during follow-up examination. Additionally, early supplementation of active TH in CRF patients with low T3 levels may improve prognosis by reducing mortality. Thus, the main focus of treatment should be on managing the primary illness and periodically reviewing thyroid functions. Taking all factors into account, recent guidelines do not recommend TH replacement therapy without clinical signs of hypothyroidism (8,39,42,46–49).

Following hospital discharge of prior critically ill patients, it is recommended to wait at least six weeks before reevaluating thyroid function. The delay allows for thyroid axis recovery and aids in differentiating between overt hypothyroidism indicated by persistent abnormal TSH levels and euthyroid sick syndrome with normalization in TSH and T3 concentrations (42).

Approaches to treatment, utilizing synthetic TH that selectively target thyroid hormone receptor ß, like GC-1, may offer beneficial metabolic effects for uremic patients, particularly by avoiding adverse outcomes such as skeletal muscle loss and tachycardia (15).

1.3 Chronic kidney disease

According to the KDIGO guidelines 2024, CKD is defined as "abnormalities of kidney structure or function, present for a minimum of 3 months, with implications for health" (50). Given the asymptomatic nature of CKD, eventually, with disease progression, the renal impairment will require replacement therapy, either through dialysis or kidney transplantation (7,51).

For the diagnosis of CKD a combination of decreased GFR and the degree of albuminuria must be considered (50).

1.3.1 Epidemiology

The European Renal Association, International Society of Nephrology and American Society of Nephrology, statetd that the global prevalence of CKD is on a rise, with approximatly 850 million affected patients in 2021, yielding almost 10% of worldwide disease prevalence

(50)S137. This increase is correlated with the rise of risk factors contributing to CKD including diabetes mellitus, hypertension and obesetiy (7). Disability-adjusted life-years (DALYs) were estimated at 35.8 million in 2017 and increased to 41.5 million in 2019. CKD related anual deaths have been rising from 1.2 million in 2017 to 1.43 million in 2019. Those most affected, have been within the 3 lowest quiantiles of the sociodemographic index (SDI) (50).

1.3.2 Pathogenesis

CKD is characterised by progressive damage to the kidneys, typically resulting from common conditions such as hypertension, obesity, and type 2 diabetes mellitus. This ongoing damage ultimately leads to fibrosis and structural destruction of the renal tissue. The structures affected are the glomeruli, tubules, interstitium and vessels, giving rise to glomerulosclerosis, tubulointerstitial fibrosis and vascular sclerosis. On a cellular level, inflammatory cells infiltrate the tissue, causing altered activity of renal cells such as apoptosis and necrosis. This process further induces proliferation of myofibroblasts and fibroblasts, creating structural disruption due to excessive production of extracellular matrix (51,52).

1.3.3 Clinical Manifestations

The asymptomatic nature of CKD favors silent disease progression, potentially leading to renal failure in months to decades, if left untreated. When symptoms appear, they can vary widely and are mostly marked by fatigue, lack of energy, drowsiness, pain and prutirus. Severe symptoms, however, correlate with kidney failure and can encompass symptoms including anemia, uremia, electrolyte abnormalities, volume overload, acidemia, mineral and bone diseorders, and can even become life-threatening without appropriate medical intervention (51,53,54).

CKD is inherently a systemic disease that influences multiple organ systems. The activation of the sympathetic nervous system due to its stressful nature, potentiates a pro-inflammatory state, leading to the accumulation of reactive oxygen species (ROS). This activation amongst other effects, may promote hypertension which can result in left ventricular hypertrophy, fibrosis, and eventually heart failure. Sodium retention further excarerbates these conditions. The risk of cardiovascular complications is particularly elevated in stages 3-5 of CKD (55).

Moreover, CKD likely disrupts the balance between energy supply needed for immunity causing metabolic and immune malfunction. Insulin resistance alongside high inflammatory markers arise in late stages of CKD. On top of the inflammatory state being a promotor of the systemic nature of CKD, decreased cytokine clearance, infections, oxidative stress and hypoxia

further contribute to the systemic side effects. Thus, a common complication is protein-energy wasting and sarcopenia (55–57).

Furthermore, bone and mineral metabolism are affected, giving rise to chronic kidney disease-mineral bone disorder (CKD-MBD) which is characterized by disturbed levels of phosphate, calcium, parathyroid hormone (PTH), vitamin D, and fibroblast growth-factor 23 (FGF23). This in turn may lead to renal osteodystrophy, vascular calcifications and cardiovascular death (55,58–60).

Additionally, pulmonary hypertension and lung congestions, neurologic complications including cognitive disorders and sleep apnea may also arise (55,61–63).

1.3.4 Classification and Staging

The classification of CKD occurs based on cause, GFR division (G1-G5) and levels of albuminuria (A1-A3). Although current measurment of GFR using serum creatinine (SCr) has been viewed as appropriate, it has limiting validity. Factors linked to decreased muscle mass, particularly encounterd in CKD and atypical body composition lower prognostic value. Therefore the additional measurement of cystatin C may provide a more accurate picture, taking into account that this marker has decreased informative value in thyroid disease, cancer and steroid use. Thus, a combination of both cystatin C and SCr are preferred for eGFR. Staging occurs based on GFR and degree of albuminuria and is illustrated in detail in Figure 1 below (50,64).

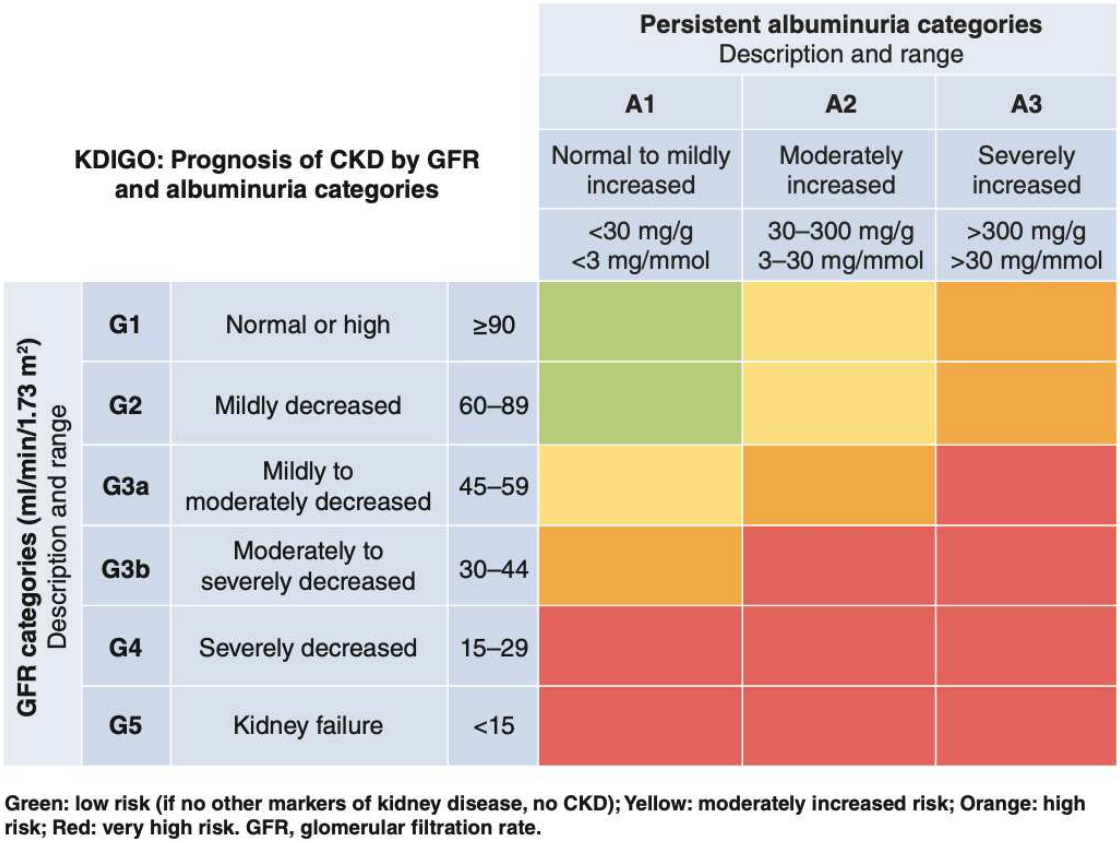

Figure 1 Current chronic kidney disease (CKD) nomenclature used by KDIGO. Source: Stevens PE, Ahmed SB, Carrero JJ, Foster B, Francis A, Hall RK, et al. KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney Int. 2024 Apr 1;105(4, Supplement):S116

1.5 The interrelation between thyroidal dysfunction and chronic kidney disease

Thyroid abnormalities interrupt proper kidney development and physiology, while renal disease will lead to thyroid dysfunction. Therefore, interdependence between both renal and thyroidal function and dysfunction exist in a bidirectional manner (65).

According to Punekars findings, a link between severity of CKD and prevalence of thyroid abnormalities are evident. Iodide excretion is primarily navigated by glomerular filtration and is therefore compromised in advanced kidney disease, consequently resulting in an increased plasma concentration of iodide and an initially elevated thyroidal uptake. This may inhibit the production TH through a negative feedback loop encompassing the pituitary-thyroid axis as well as the peripheral metabolism, also known as the Wollf-Chaikoff effect. Because of that, higher rates of clinical and subclinical hypothyroidism are seen in patients with CKD (66–69).

On the other hand, the arise of renal disease in hypothyroidism may be triggered by insufficient TH activity leading to lower renal blood flow, reduced GFR and tubular dysfunction. Additionally, the impaired systolic and diastolic cardiac function due to TH deficiency causes decreased cardiac output and vasodilator activation. This in turn favors alterations in intra-renal hemodynamics including RAAS and an upregulation of the tubulo-glomerular feedback (68,70,71).

Furthermore, a recent 10-year cohort study by Endo et. al. concluded an increased risk of CKD development at high concentrations of TSH. The risk was specifically seen in men compared to women (72).

2. OBJECTIVES

2. 1 Aims of the Study

The primary aim of this study was to observe discrepancies in the conversion rate of thyroid hormone parameters fT4 to fT3 between CKD stage 2 and CKD stage 4 patients. This was assessed using fT3/fT4 ratio, SPINA GD values and the occurrence of fT3 values below reference range.

The secondary objective was to compare TH levels between subgroups of CKD stage 2 and stage 4 patients who are undergoing TH replacement therapy with levothyroxine and those who are not receiving any thyroid hormone medication.

2. 2 Hypotheses

1. The conversion rate of fT4 to fT3, as indicated by the fT3/fT4 ratio and SPINA GD, is significantly reduced in CKD stage 4 patients compared to CKD stage 2 patients.
2. Patients with CKD stage 4 are more likely to have fT3 levels below the reference range compared to those with CKD stage 2.
3. Thyroid hormone levels differ significantly between CKD stage 2 and CKD stage 4 subgroups that are receiving levothyroxine therapy compared to those not receiving it.

3. MATERIALS AND METHODS

3.1 Study Design and Subjects

This retrospective observational study analyzed laboratory values and records of patients with CKD stages 2 and 4. Data were extracted and pseudonymized from the REGIOMED ORBIS system, focusing on patients who had thyroid function tests conducted concurrently with other routine blood tests. Furthermore, the dates of the laboratory values were chosen to be as close as possible to the medical reports from the respective hospital stays. Subjects were hospitalized at the regional clinics of Coburg and Hildburghausen in Germany.

3.2 Data Collection

The database was selected based on the international statistical classification of diseases and related health problems (ICD) of patients with CKD stage 2 (ICD: N18.2) and CKD stage 4 (ICD: N18.4) over a specified period from 1. January 2020 to 31. July 2023. Patient records were reviewed to apply inclusion and exclusion criteria and to assess pre-existing illnesses, focusing on thyroidal diseases. Electronic laboratory results and medical reports provided the collected information. For determination of comorbidities and pre-existing conditions, specifically thyroidal diseases, validated medical reports were thoroughly reviewed. Relevant information was extracted from these reports to categorize the subjects accordingly.

3.3 Inclusion and Exclusion Criteria

Patients diagnosed with CKD stages 2 and 4 based on ICD categorization in the hospitals ORBIS system were included. Since fT3 and fT4 are seldom part of check-up in routine blood testing, only those who had TSH, fT3 and fT4 measured at the same day were considered.

The initial study population consisted of 220 patients. However, after a detailed review of patient records, exclusions were applied to ensure data accuracy and relevance. Six patients were excluded due to a history of or current undergoing dialysis treatment, and nine patients with documented thyroidectomies or hemithyroidectomies. In six cases, the laboratory parameters of TSH were taken on different dates than fT3 and fT4, leading to exclusion. To reduce temporal bias, laboratory testing and discharge letters must not have been more than 3 months apart, eliminating nine more patients. Seven subjects under treatment with Thiamazole had be excluded due to its inhibitory action of TH synthesis. This reduced sample size to 183. The criteria ensured that only patients with consistent and reliable laboratory data were included in the final analysis.

3.4. Measurements

TH parameters, including TSH, fT3, and fT4, were measured in the hospital of Coburg using the electrochemiluminescence technology. Until December 22, 2022, the Cobas e601 device from ROCHE Diagnostics GmbH (Mannheim, Germany) was used, with the following reference values: TSH: 0.27-4.9 µU/mL, fT3: 3.1-6.8 pmol/L, and fT4: 12,0-22,0 pmol/L. After this date, the device was changes to the Abbott Alinity i from Abbott Laboratories (Abbott Park, Illinois, USA). The reference levels remained unchanged after the switch.

For a subset of patients form the Hildburghausen hospital, thyroid parameters were initially determined using the Cobas e601 device until 2021. Afterwards, the laboratory analysis were forwarded to Coburg hospital for further evaluation.

3.5 Groups and Subgroups

The analysis included the total study population of 183, which was further divided into two main groups: subjects diagnosed with CKD stage 2 and CKD stage 4, comprising 90 and 93 patients respectively.

Additionally, within each of these two groups, four subgroups were created to differentiate patients based on whether they were receiving levothyroxine. 21 patients with CKD stage 2 received levothyroxine, while 69 of them did not. Within the CKD stage 4 group, 32 participants were on TH substitution and 61 were not.

3.6 Statistical Analysis

The statistical analysis was done with the software program JMP pro 17, Version 17.2.0 (SAS Institute Inc., Cary, North Carolina, USA).

Shapiro Wilk and Anderson Darling hypothesis testing was used to determine normality distribution of data, aided by histograms and Q-Q plots. To examine the activity of peripheral deiodinases, SPINA GD calculation was utilized using the formula provided by Dietrich et al. The formula is as follows: SPINA GD = ((8*10^- 6)*(500+(FT4*10^-12))*(1+((2*10^9)*300)*(FT3*10^-12))/(0,026*(FT4*10^-12)))*(10^-9). Reference levels for the respective results are predefined by the essay and range between 20-60 nmol/L (73). For skewed data, results are presented as medians with interquartile ranges (IQR). Normally distributed numeric variables are described as means and standard deviation (SD). Categorical variables are defined as frequencies and percentages. Homogeneity of variance was examined for normally distributed variables using Levene's test.

Differences between CKD stage 2 and CKD stage 4 groups were analyzed using the Wilcoxon Two-Sample Test for skewed variables and Student's T-Test for normally distributed

variables. The Chi-square test of independence was used to examine the relationship between categorical variables. To examine the association between categorical variables, Fisher's Exact Test was employed.

For further analysis of the four subgroups, Kruskal-Wallis Test with Chi-Square approximation was utilized for non-normal data, while ANOVA was used for normally distributed data. Significant ANOVA results were followed by post-hoc analysis using Tukey Kramer method to adjust for multiple comparisons. Cohen's d was manually calculated for effect size if significant differences were found. Statistical significance was set to $p < 0.05$.

3.7 Ethical Approval

This study received ethical approval from the Institutional Review Board of the REGIOMED Medical School on 19th February 2024. All patient information was pseudonymized and handled in accordance with the World Medical Association Helsinki declaration of 2013. Data confidentiality was maintained in compliance with data protection regulations.

4. RESULTS

4.1 Description of Study Populations

4.1.1 Characteristics of Subjects and Biochemical Data

The study included a total of 183 patients diagnosed with CKD. Subjects were grouped according to the ICD classification of the hospital system ORBIS into a nearly equal distribution of CKD stage 2 (49.18%) and CKD stage 4 (50.82%). The median age of the study population was 80 years, with an interquartile range (IQR) of 12 years amongst which 50.82% included female and 49.18% male. Detailed demographic data and biochemical data of TH levels are illustrated below in Table 1 and 2.

Table 1: Total population and group characteristics

	Total Sample	[a]CKD Stage 2	[a]CKD Stage 4
N	183	90	93
Age (years)	80 (73-85) [46-82]	80 (72-85) [49-93]	80 (74-85) [41-92]
Female (%)	50.82	42.22	59.14
Male (%)	49.18	57.78	40.86
[e]TSH (µU/mL)	1.58 (0.69-4.84) [0.08-12.85]	1.56 (0.68-4.89) [0.07-9.50]	1.56 (0.67-4.78) [0.07-17.63]
[c]fT3 (pmol/L)	3.17±0.96 [3.03-3.31]	3.49±0.98 [3.28-3.69]	2.89±0.85 [2.69-3.04]
[b]fT4 (pmol/L)	16.92 (12.53-19.62) [10.40-27.49]	16.96 (14.36-19.49) [11.04-27.00]	16.54 (14.32-19.91) [8.87-30.75]
[c]fT3/[b]fT4 (pmol/L)	0.19±0.06 [0.18-0.20]	0.21±0.07 [0.19-0.22]	0.17±0.05 [0.16-0.18]
SPINA GD (nmols/s)	26.82±7.16 [25.77-27.86]	28.59±7.16 [27.09-30.09]	25.09±6.75 [23.70-26.49]

Data are presented as medians with IQR (Q1-Q3) in parentheses, means±SD, frequencies (percentage), and 95% CI in brackets
[a]Chronic kidney disease
[b]Free thyroxine
[c]Free triiodothyronine
[d]Levothyroxine
[e]Thyroid stimulating hormone

Table 2: Subgroup characteristics

	[a]CKD 2 [d]L-T4 yes	[a]CKD 2 [d]L-T4 no	[a]CKD 4 [d]L-T4 yes	[a]CKD 4 [d]L-T4 no
N	21	69	32	61
Age (years)	80 (77-85) [60-92]	80 (72-85) [45-94]	77 (71-84) [29-93]	82 (77-85) [51-91]
Female (%)	47.62	40.58	62.50	57.38
Male (%)	52.38	59.42	37.50	42.62
[e]TSH (μU/mL)	4.56 (0.22-5.65) [0.05-62.40]	1.5 (0.71-4.56) [1.76-5.62]	3.37 (1.08-5.62) [0.05-20.10]	1.11 (0.53-2.94) [0.08-15.39]
[c]fT3 (pmol/L)	3.16±1.04 [2.68-3.63]	3.59±0.95 [3.36-3.81]	2.68±0.76 [2.41-2.96]	2.97±0.88 [2.74-3.19]
[b]fT4 (pmol/L)	16.54 (13.04-20.99) [11.49-27.95]	17.05 (14.75-18.96) [10.83-24.01]	17.5 (14.04-20.71) [7.77-31.92]	16.54 (9.72-19.39) [9.72-30.67]
[c]fT3/[b]fT4 (pmol/L)	0.19±0.07 [0.15-0.22]	0.22±0.06 [0.20-0.23]	0.16±0.06 [0.14-0.18]	0.17±0.05 [0.16-0.19]
SPINA GD (nmols/s)	26.50±7.95 [22.88-30.12]	29.23±6.84 [27.59-30.88]	24.36±8.31 [21.36-27.36]	25.48±5.81 [23.99-26.97]

Data are presented as medians with IQR (Q1-Q3) in parentheses, means±SD, frequencies (percentage), and 95% CI in brackets
[a]Chronic kidney disease
[b]Free thyroxine
[c]Free triiodothyronine
[d]Levothyroxine
[e]Thyroid stimulating hormone

4.1.2 Thyroidal pathologies

Out of the total population of 183 patients, 75 (40.98%) had a prior diagnosis of thyroidal diseases. Among these, 29 (38.67%) had CKD stage 2, while 46 (61.34%) had CKD stage 4. Within the CKD 2 group, two patients had concurrent hyperthyroidism and struma nodosa. On the other hand, CKD 4 group exhibited simultaneous occurrence of hyperthyroidism and struma

nodosa once, hypothyroidism and struma nodosa twice, hyperthyroidism and struma diffusa once, hypothyroidism and struma diffusa once and finally hypothyroidism and Hashimoto's thyroiditis once.

The overall breakdown of thyroid conditions in the entire population is as follows: 32.79% hypothyroidism, 5.46% hyperthyroidism, 1.09% Hashimoto's thyroiditis, 4.37% struma nodosa and 1.09% struma diffusa.

Within the CKD stage 2 group, the prevalence of specific thyroidal illness was as follows: hypothyroidism 26.67%, 4.44% hyperthyroidism, 0% Hashimoto's thyroiditis, 3.33% struma nodosa and 0% struma diffusa. In contrast, within the CKD stage 4 group, the prevalence of thyroid condition revealed: hypothyroidism 38.71%, 6.45% hyperthyroidism, 2.15% Hashimoto's thyroiditis, 5.38% struma nodosa, 2.15% struma diffusa.

4.2 Statistical Analysis in Main Groups

No significant difference was found in age between the groups CKD 2 and CKD 4 ($Z = -0.0573$, $p = 0.95$) using the Wilcoxon Two-Sample Test.

The chi-square test of independence revealed a significant association between gender and CKD group ($\chi^2 = 5.238$ $p = 0.022$) with CKD2 having a higher proportion of males (57.78%, [95% CI: 0.45-0.65]) compared to CKD4 (40.86%, [95% CI: 0.47-0.67]). Fisher's Exact Test confirmed the chi-square results, indicating a significant difference in gender distribution across CKD groups (two-tailed $p = 0.027$). The left-tailed p-value (0.016) suggests that the probability of being male is significantly greater in CKD2 compared to CKD4.

Median TSH values were within reference ranges for both groups, with no significant difference according to Wilcoxon Two-Sample Test ($Z = 0.06839$, $p = 0.946$). Similarly, median values of fT4 were within reference range, and no significant difference was found ($Z = -0,25684$, $p = 0.797$).

A significant difference in mean fT3 levels was found between CKD stages through Student's T-Test ($p < 0.001$, [95% CI: -0.88608 to -0.35070]), with CKD4 showing lower fT3 levels (2.98±0.85) compared to CKD2 (3.49±0.98). The fT3/fT4 ratio was also significantly lower in CKD4 (0.17±0.05) compared to the CKD2 group (0.21±0.07), ($p < 0.001$, [95% CI: -0.05633 to -0.02081]). Furthermore, SPINA GD levels revealed a significant difference between the groups ($p = 0.001$, [95% CI: -5.5312 to -1.4674]), where mean levels of SPINA GD are lower in CKD4 (25.09±6.75) compared to CKD2 (28.59±7.16). Box plots illustrating these differences are shown in Figures 2,3 and 4.

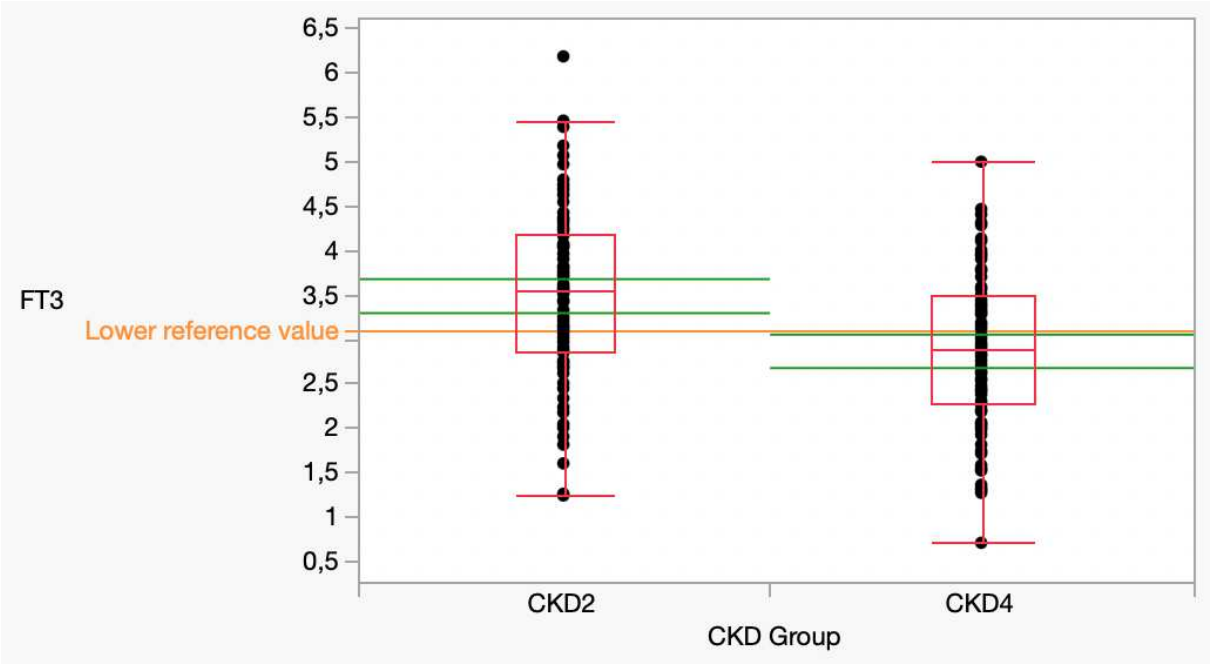

Figure 2 Box-plot representation of fT3 ratios in Groups, Green lines = [95% CI]

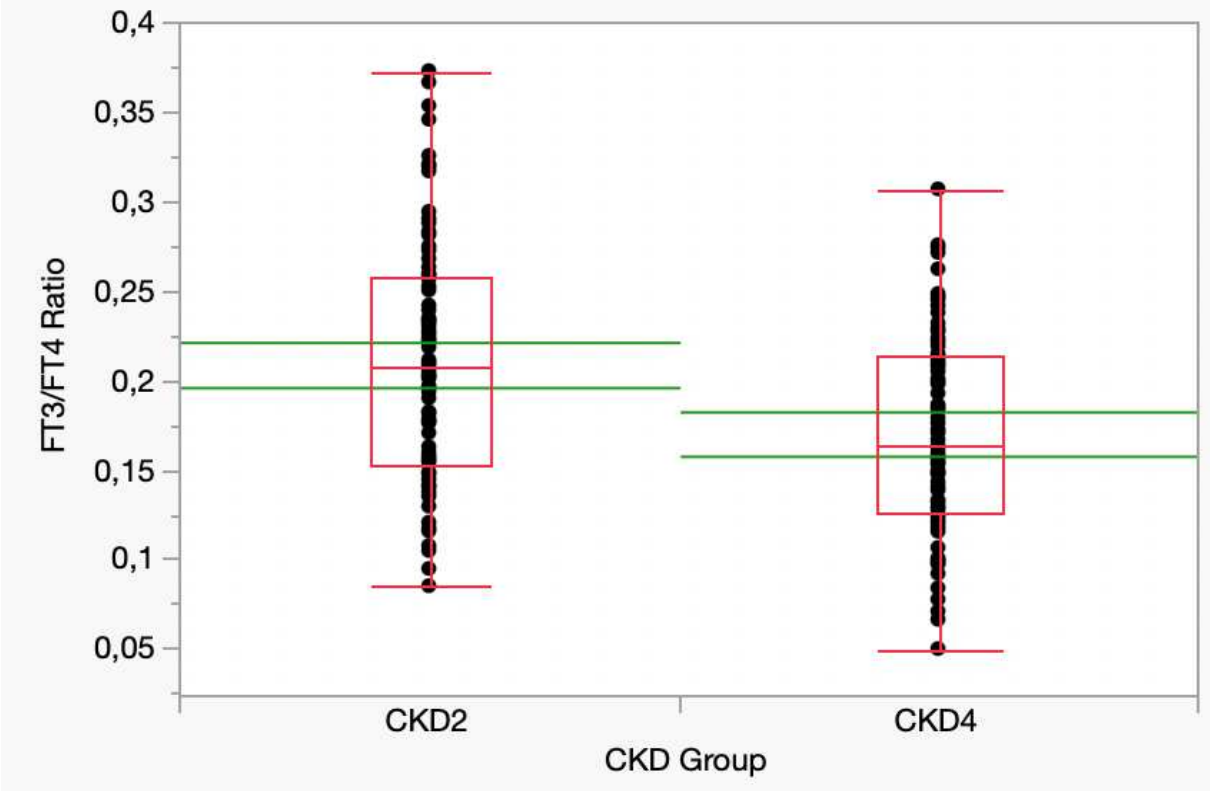

Figure 3 Box-plot representation of fT3/fT4 ratio in Groups, Green lines = [95% CI]

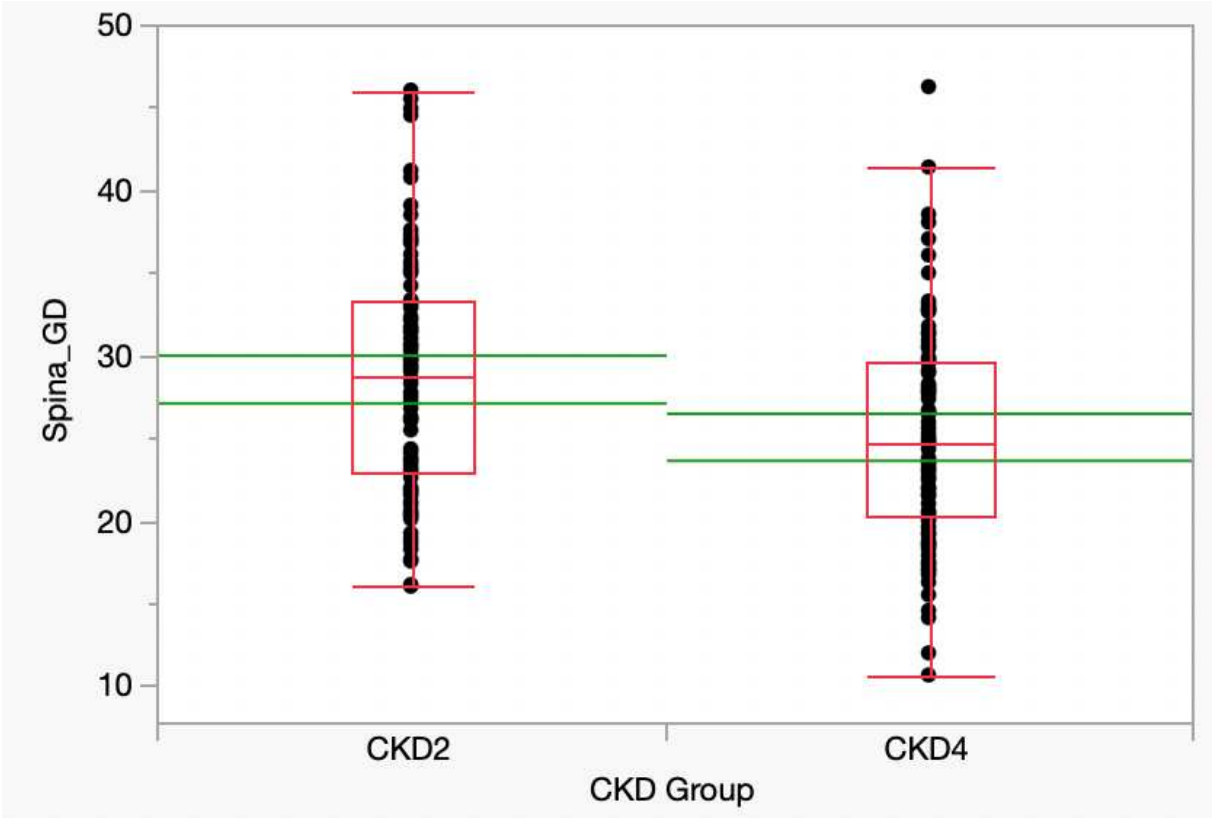

Figure 4 Box-plot representation of SPINA GD in Groups, Green lines = [95% CI]

4.3 Statistical Analysis in Subgroups

Neither the Kruskal-Wallis test for age ($p = 0.286$) nor the chi-square test for gender ($p = 0.121$) indicated statistically significant variance among the four subgroups. Likewise, Kruskal-Wallis test did not indicate a significant difference in TSH ($p = 0.079$) and fT4 levels ($p = 0.915$).

ANOVA however, revealed significant differences in fT3 levels ($p < 0.001$, $R^2 = 0.130842$, 95%). Further post-hoc analysis by Tukey-Kramer HSD method was conducted, providing adjusted p-values for multiple comparisons. Patients in CKD stage 4 that do not take L-thyroxine have significantly lower fT3 levels to those in CKD stage 2 who also take no TH medication ($p = 0.001$, [95% CI: 0.208602-1.034529]). Similarly, even if subjects with CKD4 take TH supplementation, fT3 values remain significantly lower ($p < 0.001$, 95% [CI: 0.4008-1.4059]) compared to those in CKD2 without LT-4 medication. There was no significant difference between all other subgroups. Box plot representation of said findings are shown in Figure 5.

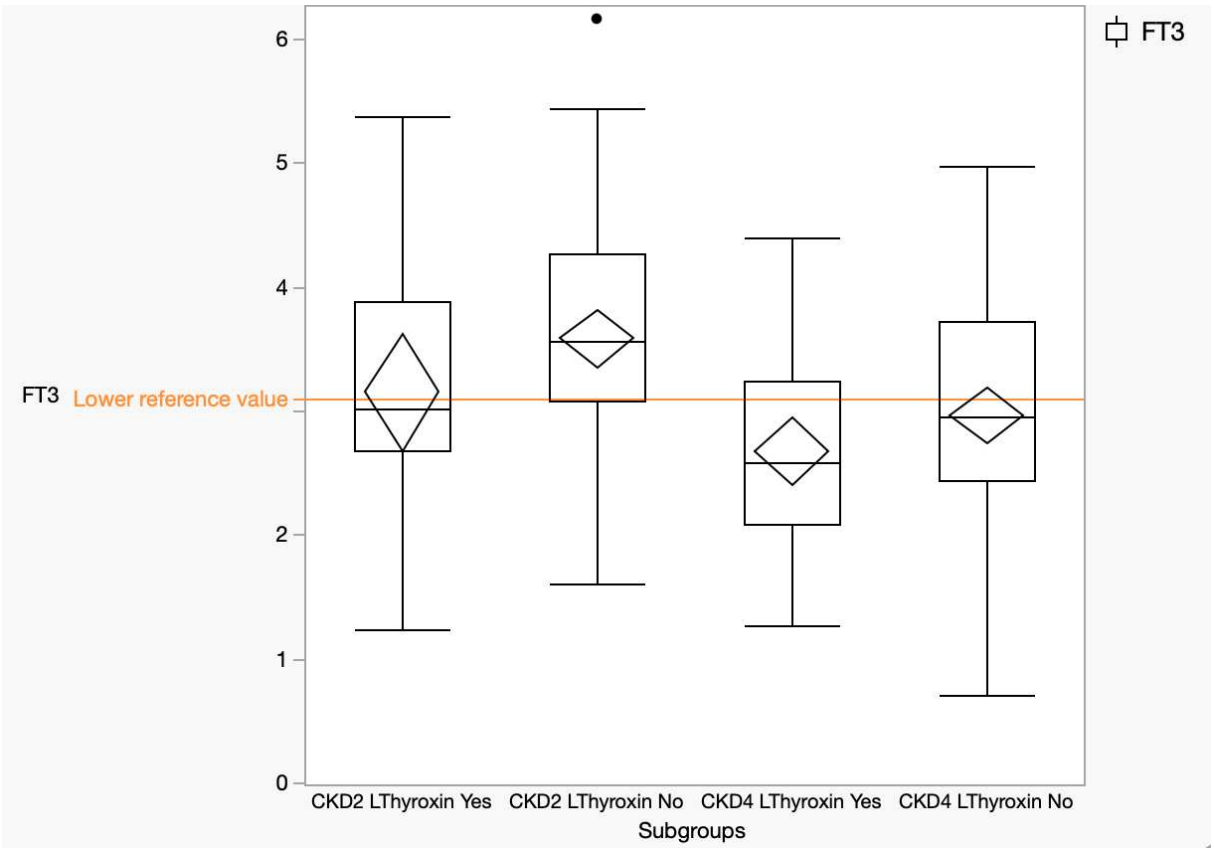

Figure 5 Box-plot representation of ANOVA for fT3 in subgroups

The one-way ANOVA indicated a significant difference in the fT3/fT4 ratio among the subgroups ($p < 0.001$, $R^2 = 0.11657$). Further post-hoc analysis using Tukey-Kramer HSD revealed that the fT3/fT4 ratio was significantly lower in CKD stage 4 compared to CKD2 subgroups, both without TH supplementation ($p = 0.001$, [95% CI: 0.013817-0.0686787]). Likewise, the ratio was significantly lower in CKD4 with L-T4 opposed to CKD2 without L-T4 ($p < 0.001$, [95% CI: 0.020279-0.0870431]). No significant differences in the fT3/fT4 ratio were found between other subgroup pairs, as their p-values exceeded 0.05.

Additionally, the analysis of SPINA GD values within the subgroups showed significant variance through ANOVA ($p = 0.003$). Specifically, SPINA GD was significantly lower in CKD4 without L-T4 compared to CKD2 without L-T4 ($p = 0.013f$, 95% [CI: 0.59062-6.914027]). Furthermore, CKD4 patients on L-thyroxine demonstrated a lower SPINA GD to patients with CKD2 but no TH supplementation ($p = 0.007$, [95% CI: 1.02429-8.719675]). All other subgroups did not reveal significant differences in SPINA GD values. Visual representation of these results is demonstrated in Figures 6 and 7.

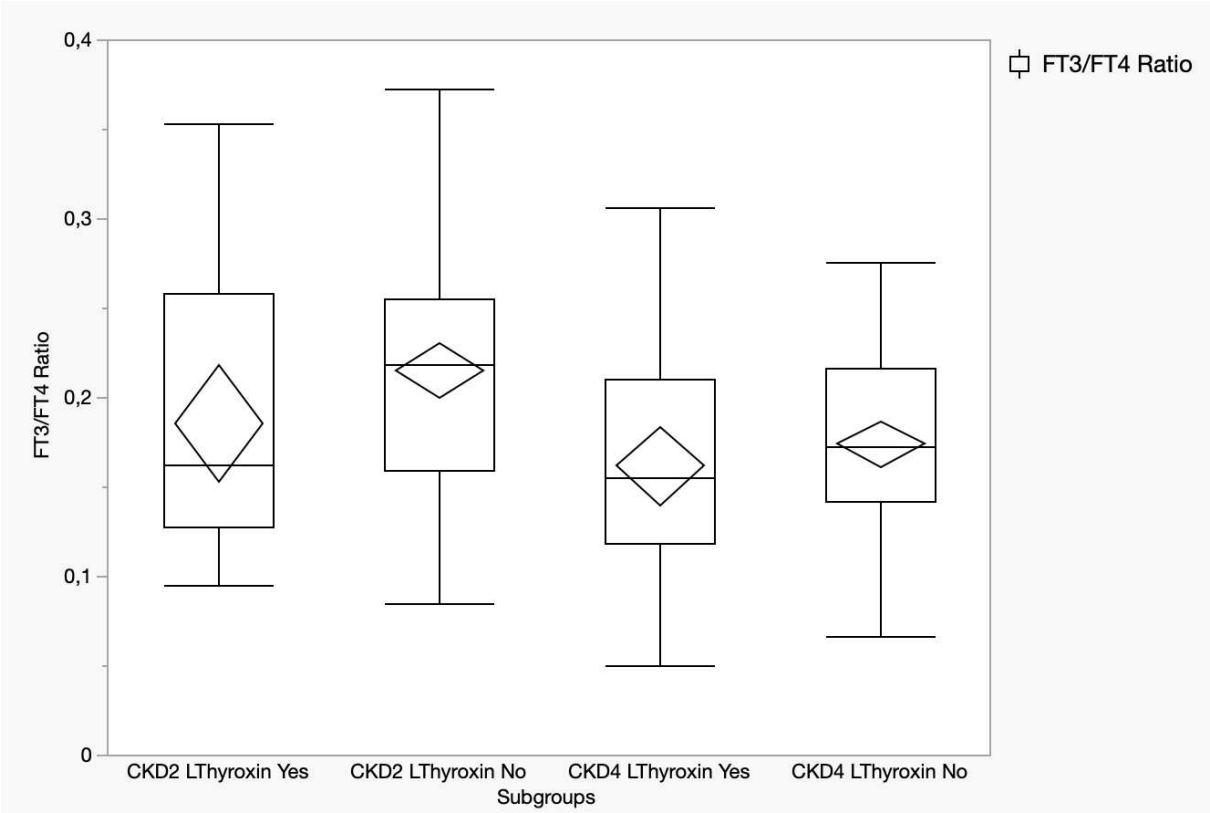

Figure 6 Box-plot illustration of ANOVA for fT3/fT4 ratio in subgroups

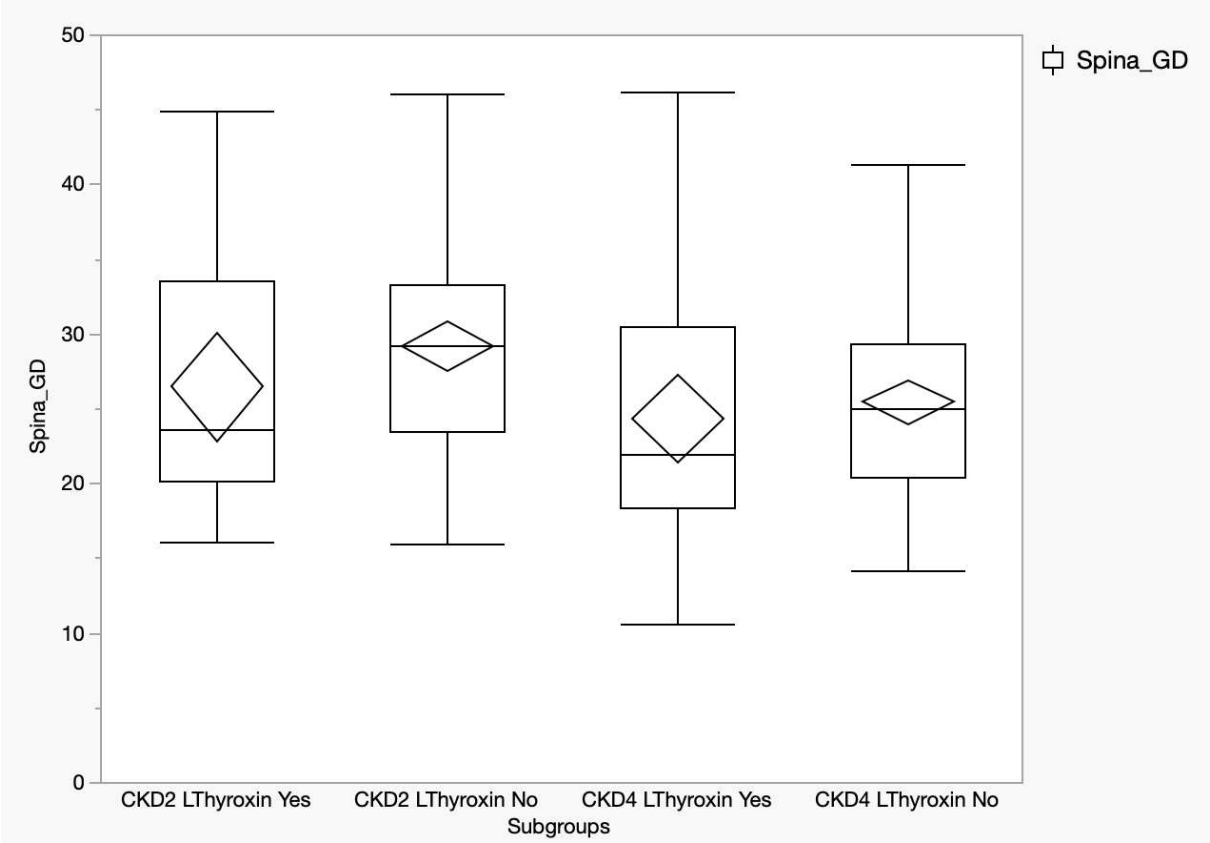

Figure 7 Box-plot illustration of ANOVA for SPINA GD in subgroups

In summary, these findings indicate that both CKD progression and L-tyhroxine treatment significantly impact the fT3, fT3/fT4 ratios and SPINA GD values. CKD4 patients, both with and without L-T4 supplementation, exhibit lower fT3, fT3/fT4 ratios and SPINA GD values compared to CKD2 patients without L-thyroxine. Therefore, these results support the occurrence of thyroidal dysfunction associated with advanced CKD.

5. DISCUSSION

Altered thyroid function associated with CKD have been reported numerously, with a predominant occurrence of NTIS, subclinical primary hypothyroidism and thyroid autoimmunity (68,74,75). We conducted a retrospective observational study to compare thyroid hormone levels in undialyzed CKD patients in stages 2 and 4.

The findings of this study showed significant alterations in TH levels as CKD progresses. In particular, fT3 levels, fT3/fT4 ratio and the SPINA GD values were lower in CKD stage 4 with the median TSH levels being within normal range (see Table 1). These results are consistent with the hypothesis that advanced CKD negatively impacts thyroid function, specifically the peripheral conversion of fT4 to fT3. Similar outcomes were observed in the cross-sectional study of Schultheiss et al. in which fT3 levels showed a negative association with eGFR. They further found that patients with said thyroid function abnormalities were at higher risk for all-cause mortality. Another study focused on TH in patients with impaired kidney function, noting a decline in fT3 levels with the progression of CKD, which closely aligns to our findings. Furthermore, research from Iglesias and Díez and Kaptein proved that NTIS is more prevalent in advanced CKD (41,76–78).

In contrast to reduced fT3, our study found that fT4 levels remained stable and within reference range across both CKD stages. This observation suggests that renal impairment may have less impact on the production of T4 by the thyroid gland compared to T3. However, most studies have found a concomitant decrease of fT4 with advanced stages of CKD (74,78).

Interestingly, the subgroup analysis revealed that even among patients receiving levothyroxine therapy, those in CKD stage 4 had significantly lower fT3 levels compared to their stage 2 counterparts. Additionally, we observed significant reductions in SPINA-GD levels in CKD stage 4, specifically among patients not receiving levothyroxine. These results correlate with the study by Carrero et al., which exposed that low fT3 levels are associated with increased mortality in dialysis patients, regardless of whether they are receiving TH supplementation (79).

Our study population revealed a higher incidence of thyroid diseases in CKD stage 4 than 2 by around 10%, however we cannot conclude which state occurred first and which one caused the other.

Given these findings, the question arises as to whether standard thyroid replacement therapy can fully compensate the deficiency of TH in advanced CKD. This is especially relevant, since the lack of active TH is likely resulting from an impaired peripheral conversion by deiodinases rather than reduced TH production by the thyroid gland itself.

Thus, alternative therapeutic strategies, such as direct T3 supplementation, might be more effective in managing thyroid dysfunction in these patients, a notion supported by previous research, including the work of Chonchol et al. (80).

Because of the asymptomatic nature of CKD, especially in its early stages, there needs to be better screening to find patients in their disease beginnings and additional research that will investigate at which stage of CKD exactly thyroid malfunctions arise.

5.1 Study limitations

Despite the significant findings, the retrospective observational nature of this study inherently limits the ability to establish causality between CKD progression and impaired thyroid function. While the study highlighted an association between advanced CKD and reduced fT4 to fT3 conversion, it cannot definitely define the directionality or causative factors underlying this relationship.

It is important to note that categorizing patients into CKD groups was based on identifying them through ICD codes in the ORBIS System of the hospitals, potentially introducing bias. According to the latest KDIGO guidelines, accurate CKD staging should involve measurement of not only serum creatinine but also serum albumin and cystatin c. However, the GFR calculation at Coburg and Hildburghausen hospitals used the MDRD formula for staging, which solely considers serum creatinine, age and gender. This formula may be less accurate in CKD patients due to the changes in muscle mass and the prevalence of sarcopenia, which can affect serum creatinine levels. Since most blood tests did not include serum albumin or cystatin c, we were unable to recalculate eGFR for adjustment (81).

Furthermore, the inclusion of participants was primarily based on the availability of thyroid laboratory values, which may introduce bias if patient documentation and reports were inaccurate or flawed.

Additionally, the study population was relatively small and confined to a single region in Germany, known for its iodide deficiency, thus limiting the generalizability of the findings to broader CKD populations.

Moreover, potential confounding factors were not accounted for, such as the use of medications affecting thyroid function (other than levothyroxine), nutritional status, the presence of comorbidities, or inflammatory markers like c-reactive protein (CRP).

Finally, while the study focused on fT3 and fT4 levels, it did not examine reverse T3 (rT3), which could provide further insights into the complex interactions between CKD and thyroid dysfunction.

Due to the oftentimes asymptomatic nature of CKD, particularly in its early stages, improved screening is essential for early disease detection and limiting its progression. Thus, future research should incorporate CKD stage 1 to identify at which degree of renal impairment the thyroidal dysfunction begins to occur. Furthermore, larger and more diverse cohorts are necessary to validate these results across different demographics and healthcare settings, while also adjusting for confounding factors.

6. CONCLUSION

This study revealed an increased occurrence of thyroid dysfunctions with disease progression of CKD as demonstrated by significant reduction in fT3 levels, fT3/fT4 ratio and SPINA-GD levels in CKD stage 4 compared to stage 2.

The values of TSH and fT4 being within reference range across the groups is indicative that the origin of TH deficiency is attributed to the impaired peripheral conversion of fT4 to fT3 by deiodinase. The reduced SPINA-GD levels in CKD stage 4 additionally support the hypothesis that peripheral deiodinase activity is diminished in advanced CKD. This altered conversion aligns with the concept of "low T3 syndrome", commonly observed in patients with advanced CKD.

Furthermore, the study found that patient with CKD stage 4, even those undergoing levothyroxine therapy, exhibited significantly lower fT3 levels compared to those in stage 2, suggesting that the standard thyroid hormone replacement therapy may not fully address the impaired conversion.

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8. SUMMARY

Objectives: The main objective of this study was to observe differences in the conversion rate of thyroid hormone parameters free thyroxine (fT4) to triiodothyronine (fT3) between patients with stages 2 and 4 of chronic kidney disease (CKD). The secondary objective was to compare thyroid hormone levels between subgroups of CKD stage 2 and 4, specifically comparing patients who received thyroid hormone replacement therapy with levothyroxine and those who did not receive any thyroid hormone medication.

Patients and methods: In this retrospective observational study, clinical data of patients admitted to the REGIOMED Hospital Coburg and Hildburghausen in Bavaria, Germany were included. CKD categorizations occurred based on the international statistical classification of diseases and related health problems (ICD) code from the hospitals Orbis System. The chosen time period of inclusion was set to 1. January 2020 to 31. July 2023. The data was pseudonymized for further use. The total study population included 183 patients, after applying the exclusion criteria to the initial 220 participants. The statistical analysis was carried out with JMP pro 17 program.

Results: This study found that patients with CKD stage 4 had significantly lower fT3 levels and a reduced fT3/fT4 ratio compared to those with CKD stage 2, indicating an impaired conversion of fT4 to fT3 in the later stages of CKD. This decrease was observed even among patients receiving levothyroxine therapy. TSH and fT4, however, did not show any significant changes amongst groups and subgroups and remained within reference range. Additionally, the study revealed lower SPINA-GD levels in CKD stage 4 patients, further supporting the hypothesis of diminished peripheral deiodinase activity in these patients.

Conclusion: The results of this research revealed significant impairment in the conversion of fT4 to fT3 in patients with advanced CKD. The decreased fT3 levels, despite levothyroxine therapy, suggest that new treatment methods may be needed for managing thyroid dysfunction and counteracting the associated increased risk for mortality in this patient population. Therefore, further research is necessary to explore the directionality of disease occurrence and to find optimal therapeutic approaches. Additionally, clinical implications of nonthyroidal illness syndrome within the different stages of CKD need to be further investigated as well as the distinct degree of renal dysfunction, leading to thyroidal abnormalities.

9. CROATIAN SUMMARY

Naslov: Retrospektivna usporedba razina hormona štitnjače u ranim i kasnim staijima kronične bolesti bubrega.

Ciljevi: Glavni cilj ove studije bio je promatrati razlike u stopi konverzije parametara hormona štitnjače slobodnog tiroksina (fT4) u trijodtironin (fT3) između pacijenata s fazama 2 i 4 kronične bolesti bubrega (KBB). Sekundarni cilj bio je usporediti razine hormona štitnjače između podskupina KBB stadija 2 i 4 među kojima su pacijenti bili na nadomjesnoj terapiji hormonima štitnjače levotiroksinom i onih koji nisu primali nikakve lijekove za hormone štitnjače.

Pacijenti i metode: U ovoj retrospektivnoj opservacijskoj studiji uključeni su klinički podaci pacijenata primljenih u REGIOMED bolnicu Coburg i Hildburghausen u Bavarskoj, Njemačka. Kategorizacije KBB-a izvršene su na temelju međunarodne statističke klasifikacije bolesti i srodnih zdravstvenih problema (ICD) kodova iz Orbis sustava bolnice. Odabrano vremensko razdoblje uključivanja postavljeno je na 1. Siječanj 2020. do 31. Spranj 2023. Podaci su pseudonimizirani za daljnju upotrebu. Ukupna populacija studije uključivala je 183 pacijenta, nakon primjene kriterija isključenja na početnih 220 sudionika. Statistička analiza provedena je s JMP pro 17 programom.

Rezultati: Ova studija je otkrila da pacijenti s KBB stadijem 4 imaju značajno niže razine fT3 i smanjen omjer fT3/fT4 u usporedbi s onima s KBB stadijem 2, što ukazuje na oslabljenu konverziju fT4 u fT3 u kasnijim stadijima KBB-a. Ovo smanjenje je zabilježeno čak i među pacijentima koji su primali terapiju levotiroksinom. TSH i fT4, međutim, nisu pokazali značajne promjene među grupama i podskupinama te su ostali unutar referentnog raspona. Osim toga, studija je otkrila niže razine SPINA-GD kod pacijenata s KBB stadijem 4, što dodatno podržava hipotezu o smanjenoj aktivnosti perifernih dejodinaza kod ovih pacijenata.

Zaključak: Rezultati ovog istraživanja otkrili su značajno oštećenje u konverziji fT4 u fT3 kod pacijenata s uznapredovalom KBB. Smanjene razine fT3, unatoč terapiji levotiroksinom, ukazuju na to da bi mogle biti potrebne alternativne strategije liječenja za upravljanje disfunkcijom štitnjače i suzbijanje povezanog povećanog rizika od smrtnosti u ovoj populaciji pacijenata. Stoga je potrebno daljnje istraživanje kako bi se istražila uzročnost pojave bolesti i pronašli optimalni terapijski pristupi. Osim toga, potrebno je dodatno istražiti kliničke implikacije sindroma bolesti koja nije povezana sa štitnjačom u različitim stadijima KBB-a, kao i specifični stupanj bubrežne disfunkcije koji dovodi do abnormalnosti štitnjače.