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Thyroid Function Test & Hematological Abnormalities in CKD

Neha Mishra[1] , Khaleel Ahmed Manik[2] , Mukhtar Ahmad[3] , Gauhar Hussain[4]
[1] Research Scholar, Department of Physiology, Integral Institute of Medical Sciences and Research, Integral University, Lucknow, India
[2,4]Department of Physiology, Integral Institute of Medical Sciences & Research, Integral University, Lucknow ,India.
[3]Department of Medicine, Integral Institute of Medical Sciences & Research, Integral University, Lucknow ,India.
Corresponding author – Khaleel Ahmed Manik, Professor, Department of physiology, Integral Institute of Medical Sciences & Research, Integral University, Lucknow ,India.
Institutional Affiliation: Integral Institute of Medical Sciences & Research, Integral University, Lucknow ,India.

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ABSTRACT:
The clinical illness known as chronic kidney disease (CKD) is typified by the permanent loss of kidney function. It is a common illness that affects people all around the world. Thyroid hormone, and thyroid-stimulating hormone (TSH) metabolism, breakdown, and removal are all greatly aided by the kidneys. Thyroid dysfunction can also arise as an endocrine symptom in patients with CKD. The results of earlier research examining thyroid anomalies and severity of CKD have been inconsistent. Based on epidemiologic data, there is a progressive increase in the prevalence of hypothyroidism as kidney failure severity increases. Owing to changes in thyroid hormone production, metabolism, and control, a variety of abnormalities in thyroid functional tests are also frequently seen in patients with CKD. Although the exact mechanism between thyroid and kidney disease is yet unknown, observational research indicates that hypothyroidism is linked to aberrant kidney shape and function. Recent research indicates that hypothyroidism, once believed to be a physiological response, is linked to an increased risk of cardiovascular disease and death in those with chronic kidney disease. A typical side effect of chronic renal disease that has a high morbidity and death rate is anaemia. The majority of chronic renal failure patients have significant anaemia and bleeding tendencies at first, which get worse when they have underlying medical conditions. In addition to haemoglobin hematocrit (Hct), CKD is characterised by abnormalities in red blood cell (RBC), total leukocyte count (TLC), and platelet count. An increasing amount of research indicates that haematological abnormalities and thyroid dysfunction are risk factors for incident CKD, the advancement of CKD, and an increased risk of death in individuals with renal disease. Thorough research is required to ascertain how thyroid hormone blood parameters affect the course and mortality of kidney disease, since this could provide insight into the potential causative relationships between these and CKD.

Introduction

A range of pathophysiologic events linked to aberrant kidney function and a persistent decrease in glomerular filtration rate (GFR) are together referred to as CKD. Based on the estimated GFR, there are five stages of CKD. Chronic renal failure (CRF), which is associated with stages 3 to 5 of CKD, is defined as an irreversible decrease in the number of nephrons.[1] According to the Kidney Dialysis Outcomes Quality Initiative (K/DOQI) guideline of the US National Kidney Foundation, the estimated GFR for CKD is three months. 2 Stage-V CKD is known as end stage renal disease (ESRD), when GFR is less than 15 ml/min/1.73 m2, necessitating dialysis or renal replacement therapy.[2]

The majority of inhabitants worldwide suffer from CKD. According to global burden of disease (GBD), there were 698 million instances of chronic kidney disease (CKD) worldwide in 2017, representing a

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9% adult prevalence rate.[3] 35.8 million disability-adjusted life years (DALYs), 28.5 million years of life lost (YLLs), and 7.3 million years lived with disability (YLDs) were caused by CKD. In 2017, China and India accounted for one-third of the global cases of CKD, with 132.3 and 115.1 million cases, respectively.[4]

Obesity, diabetes mellitus, and hypertension are main risk-factors for CKD. As CKD worsens, changes in biochemical and haematological markers become increasingly noticeable. Since the kidneys are essential for maintaining proper bodily fluid balance, electrolyte balance, and acid-base stability, CKD and end-stage renal disease (ESRD) are known to cause multiple derangements, including hyperphosphatemia, metabolic acidosis, and hyperkalaemia. Serum Zn levels were ignorantly reduced and serum P levels were ignorantly elevated in hypothyroidism cases. The serum Zn and serum P both may act as predictors for hypothyroidism and its complications.[5] These complications can lead to severe consequences, including vascular calcification, bone-mineral disorders, muscle atrophy, and death. Biochemical factors such as sodium, potassium, calcium, magnesium, and chloride should be maintained within a healthy range because their deviation might be fatal.[6,7]

Another such structure that influences almost every organ system in the body is the thyroid gland, whose functions are intimately linked to those of the kidneys. A higher frequency of thyroid disorder was observed among diabetic patients who had a higher HbA1c, who were obese, and who had a more recent onset DM (<5 years duration). The frequency of thyroid disorder was lower among diabetic patients with foot ulcers whereas no association was observed between thyroid dysfunction and other microangiopathic complications of DM.[8] Kidney function is impacted by thyroid status from the embryonic stage onward. Thyroid hormones affect neuronal input, electrolyte management, tubular activities, and overall tissue growth. Thyroid hyper- and hypofunctions impact mature kidney function both directly and indirectly. They affect renal blood flow, the cardiovascular system, glomerular filtration, electrolyte pumps, tubule secretory and absorptive capacity, and kidney structure.[9] Subclinical hypothyroidism (SCH) along with type 2 diabetes mellitus raises the risk of nephropathy and cardiovascular problems.[10]

However, thyroid hormone, thyroid-stimulating hormone (TSH), and thyrotropin-releasing hormone (TRH) are all metabolised, broken down, and excreted in large part by the kidney.[11] Among CKD patients, thyroid dysfunction is a prevalent endocrine problem. It has been observed that with CKD, the likelihood of primary hypothyroidism and SCH increases with decreasing GFR.[12] Two inflammatory cytokines, tumour necrosis factor α (TNFα) and interleukin-1 (IL-1), inhibit the expression of type one 5' deiodinase in patients with the CKD. This enzyme is necessary for the conversion of peripheral thyroxine (T4) to triiodothyronine (T3). Low total T3 levels may potentially be a result of reduced protein binding and metabolic acidosis in CKD patients.[13]

A few studies have suggested that occurence of thyroid anomalies in CKD ranges from 13% in early CKD to 70.0% in ESRD.[14,15] Nevertheless, inconsistent findings from earlier studies have left many patients' diagnoses and courses of treatment unclear. Since there is currently a dearth of worldwide data on the screening and prevalence of the thyroid disease in patients with the CKD, thyroid dysfunctions frequently go undiagnosed in CKD patients, leading to a variety of comorbidities.

In CKD, a number of haematological indices are abnormal, including haemoglobin (Hb), hematocrit (Hct), red blood cell (RBC) count, total leukocyte count (TLC), and platelet count. These changes are brought on by aluminium toxicity from hemodialysis and marrow suppression from residual uremic products. The main cause of anaemia in CKD is decreased erythropoietin production from the kidney, which results in diminished erythropoiesis. Hemolysis, prolonged blood loss, malnutrition, inflammation, and hyperparathyroidism are additional causes of anaemia.[16,17]

Therefore, the goal of this investigation is to identify any abnormalities in the patient's hematocrit as well as thyroid function as soon as possible. Patients' lives are prolonged and their mortality is decreased because it aids in early treatment and lowers patient morbidity. Quality of life in individuals suffering from chronic renal failure is significantly impacted by their haematological profile. Therefore, research on the numerous thyroid and haematological abnormalities in CRD patients is necessary.

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Hypothyroidism: The Common Yet Under Recognized Endocrine Disorder in the Kidney Disease.

Although there has been a focus on other endocrine disorders associated with CKD, like diabetes and secondary hyperparathyroidism, large observational studies reveal a significant prevalence of hypothyroidism in individuals with renal disease. A higher prevalence of hypothyroidism (defined as TSH >4.5 mIU/L or receipt of exogenous thyroid hormone supplementation) was found among 14,623 participants in the Third National Health and Nutritional Examination Survey (NHANES III) reported that "among those with cumulative severity of the kidney dysfunction: 5, 11, 20, 23, and 23% with estimated glomerular filtration rates (eGFRs) of ≥90, 60–89, 45–59, 30–44, and <30 ml/min/1.73 m^2, respectively".[18] Participants with eGFRs <30 ml/min/1.73m^2 showed a 2-fold increased risk of hypothyroidism than with eGFRs >90ml/min/1.73m2, even after adjusting for alterations in the age, gender, and race or ethnicity. In a more recent study, 23.0% of 461,607 US veterans with Stages 3 to 5 CKD (164% of the cohort) who had their serum TSH tested between 2004 and 2006 had hypothyroidism (classified as TSH >5.0mIU/L or receiving exogenous thyroid hormone replacement).[19] A significant fraction of cases in all these investigations have been attributed to subclinical hypothyroidism. Subclinical illness accounted for 56% of hypothyroid patients in the previously cited NHANES III investigation.[18] Additionally, it was discovered in Italian research of 3089 ambulatory people that prevalence of the subclinical hypothyroidism increased with decreasing renal function: 7.0% vs. 18.0% with eGFRs ≥90 vs. <60 ml/min/1.73m2, respectively.[20]

Although in relatively smaller cohorts, a high prevalence of hypothyroidism has also been noted in dialysis patients. Prevalence of hypothyroidism in U.S. and the Asian haemodialysis, and the peritoneal dialysis cohorts has varied from 13.0% to 25.0%.[21,22] Despite these informations, hypothyroidism remains the under-recognized in numerous advanced CKD cases, likely because of symptom overlap with uraemia (e.g., fatigue, decreased cognition, cold intolerance,).[23]

Mechanistic Links Between the Thyroid, and kidney disease:

Thyroid Functional Disease as the Risk Factor for the Kidney Disease.

Animal studies have shown that hypothyroidism negatively affects kidney size, and shape in both development, and the adulthood, even if the exact mechanism behind the relationship between thyroid, and the kidney illness is still unknown (Figure 1).[24] Chronic Kidney disease patients are also characterized by high genomic instability. This instability could be translated to high levels of genetic damage measured by the incidence of chromosomal damage (micronuclei) when their cells are challenged with ionizing radiation and could be either the cause or the consequence of renal pathologies.[25] Hypothyroidism in neonatal rats has been observed to cause a reduction in the kidney-to-body weight ratio, shortened tubular mass, and changes in the glomerular basement membrane (GBM), including thickness, enlargement of the mesangial matrix, and enhanced glomerular capillary permeability.[26,27,28] Hypothyroidism also been proposed as a cause of kidney dysfunction through a number of possible mechanisms, such as: (1) reduced cardiac output. (2) altered intrarenal hemodynamics (i.e., intra-renal vasoconstriction because of decreased vasodilator synthesis, and activity). (3) decreased renin angiotensin aldosterone production, and activity. and (4) increased tubulo-glomerular feed-back because of changes in chloride channel, and expression.[29,30,31] Indeed, in the animal studies, induction of the hypothyroidism by the thyroidectomy resulted in the reduced single nephron GFR, renal plasma flow and the glomerular transcapillary pressure.[32] Additionally, a number of case series have demonstrated that severe hypothyroidism causes elevated creatinine, decreased plasma flow, and decreased GFR as determined by gold standard isotope scans and indirect estimating equations. In these reports, exogenous thyroid hormone replacement was able to reverse the elevated creatinine and decreased GFR.[33,34]

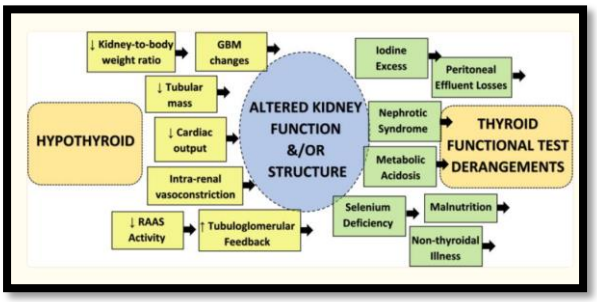

Figure-1: Proposed mechanistic links between thyroid, and kidney disease

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Abbreviations: GBM: glomerular basement membrane; RAAS: renin angiotensin aldosterone system.

Not all epidemiologic research have shown the link between renal failure and hypothyroidism. Each 10 ml/min/1.73 m2 decrease in eGFR was linked to an 18.0% increased risk of hypothyroidism in a cross-sectional examination of 461,607 US veterans who had repeated measurements of serum TSH and creatinine tests at same time periods. This association held true regardless of sociodemographic or comorbidities.[35] Kang Buk Samsung Health Study recruited 104,633 South Korean patients with normal baseline kidney function and serum TSH levels who underwent annual to biennial TSH testing. Those in highest TSH quintile (2.85–5.00mIU/L) than lowest TSH quintile (0.25–1.18mIU/L) had a 26.0% higher risk of CKD (eGFR <60 ml/min/1.73m2 using the CKD Epidemiology Collaboration formula).[36] Higher levels of TSH were linked to progressively higher CKD risk up to TSH level of ~3.20mIU/L, above which the risk plateaued. These findings, from analyses that used restricted cubic splines to examine TSH across continuous spectrum, recommend that even the high-normal TSH levels might be risk-factor for kidney dysfunction. However, not all subpopulations have shown evidence of a link between thyroid disease and CHD. Cross-sectional analyses, for instance, revealed that participants with overt, and the subclinical hypothyroidism (defined as TSH >4.5 mIU/L with free T4 levels in the low or normal range, respectively) had lower mean ± SE eGFR levels than those with normal kidney function: 53.7±2.0, 55.7±2.1, and 59.5±0.7 ml/min/1.73m2; in contrast, participants with hyperthyroidism had the highest eGFR levels: 61.5 ± 3.1 ml/min/1.73m^2.[37]

Furthermore, patients' baseline renal function was lower in those with higher TSH, and lower free T4 levels. Nevertheless, over median follow-up of five years, neither baseline thyroid functional status nor thyroid hormone concentrations were associated with changes in eGFR in longitudinal analyses. Among 309 cases of Stages 2 to 4 CKD and subclinical hypothyroidism, those who received treatment (58%) had a lower rate of eGFR decline (−2 versus −6 ml/min/1.73 m2/year, respectively), and they were less likely to have end-stage renal disease (adjusted HR [95.0% CI] 0.28 [0.12–0.68], respectively) or see a 50.0% decline in eGFR.[38] In light of sparse modifiable factors for the CKD progression, further demanding studies investigative whether thyroid hormone replacement therapy curbs kidney function trajectory in the hypothyroid CKD cases are needed.

Thyroid Functional Test Alterations in CKD:

Normal conditions involve the hypothalamic-pituitary-thyroid axis controlling the synthesis of thyroid hormones. The anterior pituitary releases TSH in response to the hypothalamus' production of thyrotropin-releasing hormone (TRH), which in turn triggers the thyroid gland's production and secretion of T4 and, to a lesser extent, T3.[39] Although the thyroid gland produces T4, type 1 and type 2 5′-deiodinase enzymes in the periphery convert T4 to T3, producing 80% of the hormone T3. T4 and T3 limit TRH and TSH by negative feedback in a multi-loop feedback system. Patients with CKD may have changes in the hypothalamic-pituitary-thyroid axis control. Furthermore, other thyroid functional test abnormalities may arise in CKD due to the kidney's involvement in metabolism, breakdown, and excretion of specific thyroid hormones and their metabolites.[40]

Thyrotropin

In general population, the serum TSH typically used for the screening, diagnosis, and treatment monitoring and the titration in the primary hypothyroidism.[41] Certain TSH changes, including reduced clearance, prolonged half-life, muted pulsatility, altered glycosylation leading to reduced bioactivity, and decreased responsiveness to TRH, may be seen in CKD.[42] It is considered the most sensitive and specific single biochemical test of thyroid function because of its inverse logarithmic correlation with serum levels of T3 and T4 (i.e., modest changes in T3 and T4 elicit exponential changes in TSH). Serum TSH is also a more reliable indicator of thyroid function in conditions other than thyroid disease.[41] Whereas low T3, and T4-levels are observed typically with mild-moderate illness, TSH typically remains normal until onset of severe, critical illness.[43]

Triiodothyronine and Reverse Triiodothyronine

Thyroid functional test alterations in individuals with CKD most frequently show low T3 levels, according to limited evidence. A study involving 2284

Journal of Chemical Health Risks
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patients with CKD and normal TSH levels revealed a progressively higher prevalence of low T3 with progressively worsening kidney function. Specifically, low levels were present in over 79% of patients with Stage-V CKD, 8, 11, 21, 60, and 79% with eGFRs ≥90, 60–89, 30–59, 15–29, and <15 ml/min/1.73m2.[44] Low T3 levels have been proposed as a marker of illness in cases with CKD because above-mentioned peripheral deiodination of T4 to T3 is reduced by the malnutrition, non-thyroidal illness, inflammation, certain medications and in presence of the high serum cortisol, and the free non-esterified fatty acid levels.[43,45]

Reverse T3 is metabolically inactive form of the thyroid hormone that produced from the precursor, T4, by type 3 5′ deiodinase enzyme.[46] This enzyme degrades reverse T3 in the inactive diiodothyronine. In the non-thyroidal illness, reverse-T3 levels typically high because of heightened production, and the reduced decomposition.[47] Reverse T3 concentrations in hypothyroidism are usually low because of decreased T4 production, albeit in mild cases, levels may be normal or high. Although reverse T3 is frequently normal in renal dysfunction, it is unclear what clinical value these levels have for interpreting thyroid function tests CKD cases.

Total and Free Thyroxine:

Since most circulating T4 is attached to proteins, including as albumin, lipoproteins, transthyretin, thyroid-binding globulin, and others, total T4 levels (which include both free and protein-bound hormone) may be erroneously low in low-protein situations.[48] Although the amount of biologically active, non-protein bound hormone can be determined using free T4 levels, commonly used free T4 assays (such as the analogue method) rely on protein-hormone binding and may not be reliable in the abnormal protein states (such as hypoalbuminemia or pregnancy) or when certain medications (such as heparin or furosemide) are present, or when substances that interfere with protein-hormone binding (such as uremic toxins) are present.[47,48] This restriction is addressed by direct free T4 tests, which employ radioimmunoassay or liquid chromatography tandem mass spectrometry to quantify free T4 and equilibrium dialysis or ultrafiltration to separate free and protein-bound T4.[49] In contrast to indirect FT4, direct free T4 levels have demonstrated more robust inverse relationships with the log of TSH in populations with both normal and altered protein-hormone binding (e.g., pregnancy),[50,51] further studies required to determine utility in classification of thyroid function, and the prognostication of outcomes in CKD.

Anemia in CKD:

Anaemia is frequent in individuals with CKD and is related with higher risk of cardiovascular events and hospitalization, progression to end-stage kidney disease, death, and poor quality of life.[52] Anaemia is twice as common in people with CKD (15.4%) as it is in general population (8.4%), according to data from the United States (US) National Health and Nutrition Examination Survey conducted in 2007–2008 and 2009–2010 and the World Health Organization's definition of anaemia, which is haemoglobin (Hb) < 3g/dl in men and < 12 g/dl in women. Anaemia is more common at each stage of CKD: 8.4% at stage 1, 12.2% at stage 2, 17.4% at stage 3, 50.3% at stage 4, and 53.4% at stage 5. Among US patients aged 65 to 88 years, the incidence of anaemia increases with stage of CKD: 43.9% at stage 3 CKD, 64.0% at stage 4, and 72.8% at stage 5.[53] Anaemia of CKD was formerly believed to be a state of EPO deficit due to the loss of EPO-producing cells. This was because the kidneys are the primary source of erythropoietin (EPO), the hormone responsible for the synthesis of red blood cells (RBCs) by the bone marrow.

Blood Cell Parameters in CKD

Along with other variables that reduce marrow erythropoiesis and shorten red cell survival, poor erythropoietin synthesis is the main cause of the reduction in these red blood cell characteristics.[16,17] The hormone erythropoietin controls the synthesis of RBC and preserves their vitality by delaying DNA cleavage. DNA breakage occurs quickly in the absence of erythropoietin and results in cell death. Even in patients with mild to moderate renal insufficiency, Hb and Hct concentrations fall with CKD as result of decreased erythropoietin synthesis and red cell destruction.[54] Additionally, erythropoietin increases the effects of paraoxonase (PON 1) and acetyl hydrolase (PAF-AH), two megakaryocyte colony promoting agents. Therefore, decreased erythropoietin synthesis in CKD results in a decrease in platelet count.[55] Reduction in TLC in CKD patients undergoing dialysis is due to complement activation which induces neutrophil aggregation and

Journal of Chemical Health Risks
www.jchr.org
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adherence to endothelial surface.[56] Suresh M et al[57] showed decreased TLC in their study similar to our study but it was not statistically significant. Other study showed increase in total leukocyte count in CKD patients.[58] In a previous study by Al-Khayat et al[59] in 2016 found that anaemia for kidney failure was closely associated with haematological parameter (WBC count and granulocyte). While Fouad M et al[60] found in Egypt research in haemodialysis patients with hepatitis C infection appears to have higher haemoglobin. Results of the Humudat YR, Al-Naseri SK[61] study show significant differences between kidney failure anaemia and some inflammation, namely RBC, MCH, WBC, lymphocyte, neutrocyte, and platelets in patients on regular HD therapy.

Conclusion

Hypothyroidism and haematological abnormalities are disproportionately more common in patients with CKD, yet many cases may go undetected. Abnormalities in a number of biochemical and haematological markers are linked to CKD. Patients with CKD must have these indicators evaluated on a regular basis. Reducing these anomalies contributes to a decrease in CKD-related morbidity and mortality. In CKD patients, anaemia is a major source of morbidity and gets worse as the condition worsens. It was discovered that the haemoglobin parameter had a weak link with MCH, WBC count, WBC differential, platelet count, and HCV infection, whereas RBC had a substantial correlation with haemoglobin in several investigations. Further mechanistic studies needed to understand pathogenesis of thyroid, and haematological functional disorders in the kidney disease, in addition to how CKD might engender both.

List of abbreviations:

CKD : Chronic kidney disease ; MCH: Mean Corpuscular hemoglobin ; MCHC: Mean corpuscular haemoglobin concentration ; MCV: Mean Corpuscular Volume ; RBC: Red blood cell ; WBC: White blood cell count ; HD : Hemodialysis ; TLC : Total leckocyte count, EPO: Erythropoietin; FT4: Free thyroxine ; FT3: Free triiodothyronine; TSH: Thyroid stimulating hormone ; eGFR : Estimated glomerular filtration rate; ESRD : Early stage renal disease ; SCH: Subclinical hypothyroidism ; HCT: Hematocrit; CRD: Chronic renal disease; GBM: glomerular basement membrane; CHD: Coronary heart disease.

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