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Review Article

A REVIEW OF THYROID DISORDERS AND ITS RELATION TO CHRONIC KIDNEY DISEASE

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ABSTRACT

Thyroid hormones have a very important role in regulating metabolism, development, protein synthesis, and influencing other hormone functions. The two main hormones produced by the thyroid are triiodothyronine (T3) and thyroxine (T4) and these hormones can also have significant impact on kidney diseases, so it is important to consider the physiological association of thyroid dysfunction in relation to chronic kidney disease (CKD). CKD has been known to affect the pituitary-thyroid axis and the peripheral metabolism of thyroid hormones. Low T3 levels or non-thyroid illness are the most common laboratory finding followed by sub-clinical hypothyroidism in CKD patients. Hyperthyroidism is usually not associated with CKD but has been known to accelerate it. One of the most important links between thyroid disorders and CKD is elevated urea levels/uremia. Patients who are appropriately treated for thyroid disease have a less chance of developing renal dysfunction. Clinicians need to be very careful in treating patients with low T3 levels who also have an elevation in TSH, as this can lead to a negative nitrogen balance. Thus, clinicians should be well educated on the role of thyroid hormones in relation to CKD so that proper treatment can be delivered to the patient.

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INTRODUCTION

Chronic kidney disease is a clinical syndrome due to irreversible renal dysfunction leading to metabolic, excretory and synthetic failure resulting in nitrogenous waste products accumulation. End Stage Renal Disease is when a patient has stage 5 CKD with glomerular filtration rate of 15 ml/min or less. In this stage kidney will have lost nearly all its functional ability, and eventually renal replacement therapy or a kidney transplant will become necessary to sustain life¹.

Thyroid Dysfunction is common in adult population. Hypothyroidism and hyperthyroidism can be readily diagnosed with laboratory tests. Thyroid disorders are classified into hypothyroid, hyperthyroid, and a subclinical state.² It was seen in earlier studies that fT3 was lower in ESRD patients than in healthy subjects.³ Even though fT3 was found to be low, fT4 and TSH were found to be within normal limits. This phenomenon is called as Non-Thyroidal Illness.³ Thyroid hormone plays an important part in growth, development and physiology of kidney.⁴ Likewise, kidney is involved in the metabolism and elimination of

thyroid hormone.⁴ Hyperthyroidism, hypothyroidism and euthyroidism have all been reported by various studies.^{2,5} Subclinical hypothyroidism is the most common thyroid dysfunction found in CKD.⁵

Patients with CKD may present with symptoms and signs suggestive of thyroid dysfunction.⁵ These findings include dry skin, edema, cold intolerance, low temperature, decreased basal metabolic rate, lethargy, fatigue and hyporeflexia. So in CKD patients, it is difficult to exclude the diagnosis of hypothyroidism on clinical grounds.⁵

METHODS

In this article, we reviewed various observational articles, clinical and experimental studies and from electronic databases (PUBMED and Cochrane Central Register of Controlled Trials) for potentially relevant articles comparing various studies from January 2010 to December 2018 published in English. Keywords used for search included: Chronic Kidney Disease, Thyroid dysfunction, Hypothyroidism, Sub-clinical hypothyroidism Non-Thyroid Illness, Renal function Test.

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EPIDEMIOLOGY

In India >1 billion population are prone for CKD which is likely to pose major problems for both healthcare and the economy in future years. Indeed, it has been estimated that age-adjusted incidence rate of ESRD in India to be 229 per million population.⁶ The numbers of CKD cases are on the rise in developing countries mainly in India and China. This rise can be attributed to the increase in life expectancy of people of developing countries.⁷ The most common cause for CKD is diabetes and hypertension. In western population about two-third of the CKD population is suffering from diabetes or hypertension or both. In Indian scenario, 40-60 percent of CKD patient are found to be suffering from at least one of the two comorbidities.⁸ As India is the diabetic capital of the world and number of hypertensives are also increasing, the estimated individuals suffering from CKD is expected to increase. These individuals with risk factors thus become the key target population to address to reduce the burden of CKD.⁹ The common cause of CKD in India is Diabetic Nephropathy. The second most common cause of CKD is chronic glomerulonephritis followed by hypertensive nephrosclerosis.¹⁰ About 48% cases presented in stage 5 and were younger (less than 40 years) than those in Stages III-IV. Diabetic nephropathy patients were older, generally presented in earlier stages of CKD at presentation. When the data of each zone was closely monitored, it was observed that south of India had the maximum cases of CKD with undetermined aetiology (20%) while East zone had least (10%).¹¹

PATHOPHYSIOLOGY

The pathophysiology of CKD involves progressive mechanisms, which results in hyperfiltration and hypertrophy of the remaining viable nephrons.^{12,13}

Intact Nephron Hypothesis¹⁴

The explanation proposed for these adaptive mechanisms is that, in CKD there is progressive loss of nephrons, so the affected nephrons are non-functioning. The remaining few functioning nephrons tend to hyper function and take an increased work load so that the overall loss of function is minimized. This indicates that GFR of the individuals non affected nephrons have increased above normal, a state known as hyperfiltration. This increase in single nephron GFR in the functioning nephrons produce an increased volume of filtrate and their tubules respond appropriately by excreting fluids and solutes in amounts which maintain external balance. This is due to close integration of glomerulus and tubular function called "glomerulo tubular balance", which is present until the terminal stages of CKD. These above stated popular mechanisms for continuing function in the remaining nephrons, is referred to as the "intact nephron hypothesis".

Classification of Ckd

Classification of CKD are many types for staging of CKD. The commonly used criteria is KDIGO classification was started in 2002. Classification and stratification was done by the American journal of kidney disease.¹⁵ In 2004 KDIGO approached with definition and classification of CKD which was modified in KDIGO 06 CC, KDIGO 09CC and KDIGO CPG on CKD in 2013.¹⁶ The 2013 Kidney Disease: Improving

Global Outcomes (KDIGO) Clinical Practice Guideline for Lipid Management in Chronic Kidney Disease (CKD) provides guidance on management of lipid and treatment for all patients with CKD. The guideline has chapters dealing with assessment of lipid status and treatment for dyslipidaemia in adults and children. The latest guidelines of KDIGO 2017 deals with Mineral bone disorder (MBD).¹⁷

Stages of ckd

Stage Description	GFR (ml/min/1.7m ²)
1. Kidney damage normal or ↑GFR □	≥90
2. Kidney damage with mildly ↓GFR	60-89 30-59
3. Moderate decrease in GFR	15-29
4. Severe decrease in GFR	<15
5. Kidney failure	

Regulation of Thyroidhormones¹⁸

In the periphery one third of T4 is converted to T3 by 5' Deiodinase and 45% to rT3 by 5 deiodinase. They are further converted to Diiodothyronine. Only about 13% of T3 is produced from thyroid gland and remaining 87% is formed from T4. The thyroid stimulating hormone (TSH) controls the secretion of T3 and T4. It is secreted in a pulsatile manner with peak secretion at night. Its secretion is stimulated by thyrotropin releasing hormone (TRH). Both TRH and TSH release are under negative feedback of free T3 and T4.

Hypothyroidism^{19,20}

Hypothyroidism is a clinical syndrome caused by decreased levels of thyroid hormones in circulation.¹² Hypothyroidism can be either primary or secondary. In primary hypothyroidism there will be an intrinsic disorder of thyroid gland and in secondary hypothyroidism there is pituitary or hypothalamic defect.

The **symptoms** of hypothyroidism in descending order of frequency are: Tiredness, weakness

1. Dry skin
2. Feeling cold
3. Hair loss
4. Difficulty in concentrating and poor memory
5. Constipation
6. Weight gain with poor appetite
7. Dyspnea
8. Hoarse voice
9. Menorrhagia (Later amenorrhea)
10. Paraesthesia
11. Impaired hearing

The signs of Hypothyroidism in Descending order of Frequency are as follows

1. Dry coarse skin
2. Cool peripheral extremities
3. Puffy face, hands and feet (myxedema)
4. Diffuse alopecia
5. Bradycardia
6. Peripheral edema
7. Delayed tendon reflex relaxation
8. Carpal tunnel syndrome

9. Serous cavity effusions.

A normal TSH level rules out primary hypothyroidism but not secondary. To diagnose primary hypothyroidism TSH level should be above 20 μ IU/ml or at least above 10 μ IU/ml if clinical features strongly suggest.

In the presence of elevated TSH, low T4 especially free T4 is necessary to confirm hypothyroidism. Circulatory free T3 is usually reduced. But it may be normal in 25% of hypothyroid patients. So T3 measurements are not reliable indicators of hypothyroidism.

Subclinical Hypothyroidism

Subclinical hypothyroidism is defined as an elevation in serum TSH concentration (normal range 5–10 μ IU/mL) in conjunction with a normal serum free T4 concentration. With the decline in GFR, the prevalence of subclinical hypothyroidism increases consistently. One study showed that approximately 18% of the patients with CKD not requiring dialysis have subclinical primary hypothyroidism. This finding is independently associated with a progressively lower estimated GFR. The prevalence of subclinical primary hypothyroidism increased from 7% to 17.9% in individuals whose GFR has decreased from \geq 90mL/min to 60mL/min.²¹ Some researchers reported that hypothyroidism can be corrected with restriction of dietary iodine in uremic patients on dialysis which decreases the need for hormone replacement therapy. In one clinical trial, the overall rate of a decline in the estimated GFR was significantly greater in those not treated with thyroid hormones compared to those who were treated with thyroid hormones.

Hyperthyroidism^{19,22}

Hyperthyroidism is a clinical syndrome which results from excessive circulating levels of free thyroid hormones.

The symptoms of Hyperthyroidism in Descending order of Frequency are as follows

1. Hyperactivity, irritability, dysphoria.
2. Heat intolerance and sweating
3. Palpitations
4. Fatigue and weakness
5. Weight loss with increased appetite
6. Diarrhoea
7. Polyuria
8. Oligomenorrhea, loss of libido

The signs of Hyperthyroidism in Descending order of Frequency are as follows

1. Tachycardia, Atrial fibrillation in the elderly
2. Tremors
3. Goitre
4. Warm, moist skin
5. Muscle weakness, proximal myopathy
6. Lid retraction or lid lag
7. Gynaecomastia

Laboratory investigations show TSH levels below normal. Free and total thyroid hormone levels are increased. In 2 to 5% of patients, only T3 is increased and T4 is normal. This condition is called "*T3 thyrotoxicosis*". Occasionally total and free T4 will be increased with normal T3 level. This condition is called "*T4 thyrotoxicosis*".

Non-Thyroidal illness^{23,24,25,26}

Thyroid dysfunction in which serum T3 is essentially affected and no underlying disease of thyroid gland is observed is variously termed as Non thyroidal illness, low T3 syndrome and sick euthyroid syndrome²³.

This Syndrome can occur in Variety of Illnesses as Follows^{23,24}:

- i. Acute critical illness and febrile illness such as infections, myocardial infarction etc.
- ii. Injuries such as burns, trauma, etc.
- iii. Surgery
- iv. Fasting
- v. Diabetes mellitus
- vi. Liver disease
- vii. Renal disease
- viii. Ketogenic diet
- ix. Drugs such as glucocorticoids, dopamine, phenytoin and beta blockers
- x. Malignancy
- xi. Psychiatric illness

As illness progresses there is a decrease in serum T4 as well, and termed as Low T3, Low T4 syndrome. Even though T3 and T4 is decreased, serum TSH remains within normal limits or slightly reduced, by which it is differentiated from primary hypothyroidism.^{25,26}

End Stage Renal Disease Presenting as Non Thyroidal illness

ESRD is one among various conditions that can cause "Low T3 syndrome". As the GFR decreases the reduction in T3 is more marked than the fall in T4. In ESRD on an average it was found that reduction in T4 is found in 29% of the patients whereas fall in T3 is found in 55 % of patients²⁷.

Pathophysiology of low T3 syndrome^{28,29,30},

There are various postulates as to how CKD can cause Non thyroidal illness. They are as follows:

Changes in Hypothalamic - Pituitary – thyroid axis

1. Due to reduced sensitivity of TSH secretion to low thyroid hormone.
2. Limited TSH reserve
3. Reduction in nocturnal pulses of TSH secretion as a result of reduced TRH secretion.

Changes in Hormone Transport

4. Presence of protein and non protein inhibitors which inhibits the binding of Thyroxine with thyroxine binding protein.
5. Alteration in the intrinsic structure of T4 binding site. Reduction in concentration of thyroxine binding globulin.
6. Changes in Metabolism
7. Decrease in action of Iodothyronine – 5 – Deiodinase which leads to low T3
8. Change in Plasma Membrane Transport
9. T3 and T4 may enter cells not only by passive diffusion but also by active energy dependant transport across plasma membrane.

10. Accumulation of following substance prevent uptake and subsequent deiodination.
 - i. 3-Carboxy 4-methyl 5- propyl 2-Furane(CMPF)
 - ii. Indoxylsulphate

Diagnosis of primary thyroid diseases inckd^{31,32,33,34}

Earlier studies have indicated that prevalence of hypothyroidism is increased in chronic kidney disease. Several clinical features of both hypothyroidism and CKD are similar. So differentiating both the conditions on clinical background is difficult. Hence all the CKD patients with symptomatology of hypothyroidism should be screened for hypothyroidism³¹.

Hypothyroidism Should Be Diagnosed Only If The Following Prevails

Basal TSH level should be elevated more than 20 μ IU/ml. Both total and free T4 are distinctly low in the presence of normal TBG. Presence of antithyroid antibodies provide a clue for hypothyroidism^{32,33}. Primary hyperthyroidism is very rare in CKD. This condition is diagnosed by low serum TSH and high serum total and free T4 concentration³⁴

Thyroid Disorders in Glomerular Diseases

Thyroid diseases including both hypo- and hyperthyroidism are associated with several types of glomerulonephritis. The types of glomerulonephritis seen in thyroid disease are membranous, IgA, mesangio-capillary, membranoproliferative, and minimal change glomerulonephritis. Among these, the most frequent is membranous glomerulonephritis concentration³⁵. The two main histological changes seen are a thickened glomerular basement membrane (GBM) due to immune complex deposition and an increased mesangial and endocapillary cellularity³⁶. The pathophysiology links between thyroid dysfunction and glomerulonephritis involve proteinuria and formation of immune complexes concentration³⁵. This association is extremely common in autoimmune thyroiditis. Approximately up to 50% of patients with autoimmune thyroiditis have the presence of immune complexes. These complexes are mainly responsible for the alteration of the renal function by depositing on the basement membrane of the glomeruli. Some studies have also reported a deposition of thyroglobulin in the basement membrane of the glomeruli. In addition to thyroid diseases, similar effects are also seen in other autoimmune disorders such as systemic lupus erythematosus (SLE) and diabetes [12].

CONCLUSION

Thyroid disorders and CKD are independently some of the most prominent medical conditions found in patients. The most common changes in CKD relating to the thyroid gland are of low T3 levels and subclinical hypothyroidism. The prevalence of subclinical hypothyroidism increases consistently in patients who have a decline in GFR. Low T3, normal to reduced T4 levels, and normal TSH often result in increased thyroid gland volume. In turn, a decrease in renal function also accounts for an ineffective clearance of abnormal serum constituents, inflammatory cytokines, iodide excretion, and an increase of nitrogen conservation. All of these factors have been clinically proven to affect the normal physiology and metabolism of thyroid hormones. Hyperthyroidism is usually not associated

with CKD but is known to accelerate it. It is very important to consider all clinical features and thyroid manifestations in those patients with CKD. As seen in many evidence-based studies and current clinical cases, there are distinct relationships in thyroid dysfunction and kidney disease and vice versa.

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