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INTERACTION BETWEEN HYPOTHYROIDISM AND CHRONIC KIDNEY DISEASE – A REVIEW

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ABSTRACT Thyroid hormones affect renal development and physiology. Thyroid hormones have pre-renal and intrinsic renal effects by which they increase renal blood flow and glomerular filtration rate. Hypothyroidism is associated with decreased GFR as well as increased renin angiotensin aldosterone activation.
Chronic kidney disease is characterized by low T3 syndrome which is now considered a part of an atypical non-thyroidal illness.
CKD patients have raised incidence of primary hypothyroidism and sub-clinical hypothyroidism. Thyroid dysfunction is also associated with glomerulonephritis by a common autoimmune etiology. There are few interactions between thyroid and renal malignancies.
A detailed knowledge of these interactions is important for both the nephrologists and endocrinologists for optimal diagnosis and management of the patient.

KEYWORDS : Chronic kidney disease, hypothyroidism, glomerular filtration rate.

INTRODUCTION:

Chronic kidney disease (CKD) is progressive loss in kidney function over a period of months or years. Chronic kidney disease is defined as either kidney damage or GFR < 60 mL/min/1.73 m^2 for 3 or more months. Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies. The most common cause of CKD is diabetes mellitus and high blood pressure. Other causes of CKD include idiopathic and glomerulonephritis. Together, these cause about 75% of all adult cases[10].

Chronic kidney disease (CKD) is becoming a serious health problem; the number of people with impaired renal function is rapidly rising, especially in industrialized countries. Recent reports, however, suggest an abrupt rise in CKD in developing countries from Asia due to increase in concomitant diseases such as type 2 diabetes, hypertension and cardiovascular diseases (CVDs). CKD is associated with a higher prevalence of primary hypothyroidism, both overt and subclinical, but not with hyperthyroidism[10].

Hypothyroidism is a disorder of the endocrine system in which the thyroid gland does not produce enough thyroid hormone. It can cause a number of symptoms, such as poor ability to tolerate cold, a feeling of tiredness, constipation, depression, and weight gain.

Thyroid dysfunction affects renal physiology and development, whereas kidney disease could result in thyroid dysfunction.

Thyroid hormones influence renal development, kidney structure, renal hemodynamics, GFR, the function of many transport systems along the nephron, and sodium and water homeostasis. These effects of thyroid hormone are in part due to direct renal actions and in part are mediated by cardiovascular and systemic hemodynamic effects that influence kidney function.

Chronic kidney disease (CKD) causes alterations in thyroid hormones in the absence of an underlying intrinsic thyroid disorder, known as the syndrome of nonthyroidal illness. This syndrome is mainly characterized by a decrease in total (T3) and free triiodothyronine (fT3) plasma concentration, whilst thyroid-stimulating hormone (TSH) levels are usually normal[10].

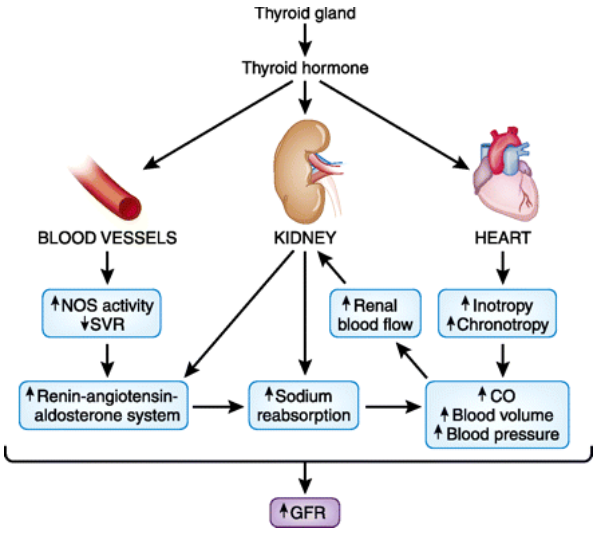
MATERIAL AND METHODS:

A search for articles using PubMed search with terms thyroid, hypothyroidism, hyperthyroidism, and renal function, glomerular filtration rate, glomerulonephritis, chronic kidney disease was performed. The most relevant and current articles were selected, retrieved in their original form or abstracts, as available. The data were analyzed to represent information from the best and current available form of evidence in the particular area.

IMPACT OF THYROID HORMONE ON RENAL GROWTH AND DEVELOPMENT:

Children with congenital hypothyroidism have reduced renal mass and a higher prevalence of renal and urologic abnormalities, including dysplastic kidney, renal agenesis, ectopic kidney, hydronephrosis, posterior urethral valves, and hypospadias. Mutations in the gene encoding *Pax8*, a transcription factor important for normal development and function, may, in some patients, be the link between congenital hypothyroidism and renal dysmorphogenesis[2].

Figure 1: Direct and indirect effects of thyroid hormones on GFR[2]



Thyroid hormone status affects the functioning renal mass (measured as the kidney to body mass ratio), with hypothyroidism reducing this ratio and hyperthyroidism increasing it.

Thyroid hormones also regulate the adrenergic receptors and dopaminergic activation of the renal tubular cells. They have been shown to affect the renin – angiotensin – aldosterone axis by adrenergic regulation, renin release, as well as influencing the angiotensinase activity. Thyroid hormones affect renal clearance of water load by their effects on the GFR. The primacy of Na/K ATPase in solute transport of the PCT is well known. Thyroid hormones influence Na reabsorption at the PCT primarily by increasing the activity of the Na/K ATPase and tubular potassium permeability. Tubular reabsorption of calcium is affected in a similar manner, but not that of magnesium[1].

Thyroid hormones also influence the neonatal renal function. Perinatal thyroid hormone status affects the mitochondrial energy metabolism enzymes in the cells of the proximal convoluted tubules (PCT). There is an increase in the activity of the Na – P co-transporter (NaPi), Na – H exchanger (NHE), as well as the Na/K ATPase in the PCT as depicted in table 1. Thus, thyroid hormones play an important role in renal development and early renal function.

Table 1 Renal tubular ion transporters affected by thyroid hormone.[2]

Na^+-K^+ ATPase
H^+-ATPase
Na^+-HCO_3^- exchanger
Na^+-H^+ exchanger
Na^+-Pi IIa exchanger
Na^+-sulfate exchanger
Na^+-K^+-$2Cl^-$ cotransporter
Na^+-Ca^{2+} exchanger
Cl^- channel
AQP 1 and 2

- Transporter function is decreased with hypothyroidism and increased with hyperthyroidism or thyroid hormone replacement with the exception of AQP, which has the opposite pattern. AQP, aquaporin.

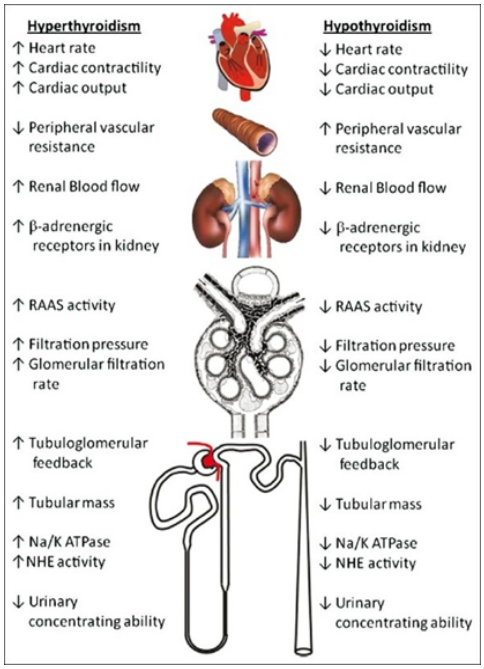
EFFECTS OF THYROID DYSFUNCTION ON THE KIDNEY

Thyroid dysfunction affects RBF, GFR, tubular function, electrolyte homeostasis, and kidney structure[2]. The various effects of hypothyroidism and hyperthyroidism on renal function have been summarized in figure 2. The effects on renal function tests are listed in Table 2.

Table 2: Clinical effects of hypothyroidism and hyperthyroidism on renal function tests[1]

Tests	Hypothyroidism	Hyperthyroidism
Serum creatinine	Increased	Decreased
Serum cystatin C	Decreased	Increased
Urinary NGAL	Unchanged	Unchanged
24-hour urine protein	Increased	Increased
Water load excretion	Decreased	Increased
Electrolyte imbalance	Hyponatremia	None

Figure 2: Effects of hyperthyroidism and hypothyroidism on renal physiology and function[1]



HYPOTHYROIDISM AND RENAL FUNCTION:

The most common kidney derangements associated to hypothyroidism are: elevation of serum creatinine levels, reduction in GFR and renal plasma flow (RPF), disruption of the capacity to excrete free water and hyponatremia.

The RBF is reduced in hypothyroidism by decreased cardiac output (negative chronotropic and inotropic effects), increased peripheral vascular resistance, intrarenal vasoconstriction, reduced renal response to vasodilators, and a reduced expression of renal vasodilators such as vascular endothelial growth factor (VEGF) and insulin like growth factor-1 (IGF-1). The GFR is reversibly reduced (by about 40%) in more than 55% of adults with hypothyroidism. There is a reduced proximal tubular absorption of sodium, chloride, and water. In addition, the renal basolateral chloride channel expression is reduced. Thus, reduced chloride reabsorption increases the distal chloride delivery, triggering the macula densa mediated tubuloglomerular feedback which reduces the RAAS activity. Consequently, the GFR falls.

There is a net reduction in sodium and bicarbonate reabsorption. An increase in sodium and bicarbonate loss in urine results in defective urinary acidification. Decreased tubular reabsorptive capacity also results in inability to maintain the medullary hypertonicity. Medullary hypertonicity is primary the driving force behind urinary concentration. Loss of medullary hypertonicity in hypothyroidism results in impaired urinary concentrating ability of the kidney. Hypothyroidism-associated kidney dysfunction seems to be more related with the decline in thyroid hormone levels rather than with thyroid autoimmunity. Among the mechanisms involved in hypothyroidism-associated kidney derangements are direct effects of TH on the cardiovascular system (increased peripheral resistance and reduction of myocardial contractility and stroke volume) and metabolism (hyperlipidemia), and indirect effects through paracrine or endocrine mediators, such as insulin-like growth factor type 1 (IGF-1) and vascular endothelial growth factor[17].

SUBCLINICAL HYPOTHYROIDISM :

Subclinical hypothyroidism is defined as an elevation in serum TSH concentration (normal range 5–10 μIU/mL) in conjunction with a normal serum free T4 concentration[3].

Reduced kidney function was associated with prevalent subclinical and clinical hypothyroidism among ambulatory adults[6]. The renin-angiotensin system plays a crucial role in the cross-talk between the thyroid and the kidney. . This information is essential as it shows a link between two separate conditions.

CKD affects the hypothalamus-pituitary-thyroid axis and the peripheral metabolism of thyroid hormone. Low T3 is the most common laboratory finding and subclinical hypothyroidism is most common thyroid disorder found in CKD patients. TSH levels are usually normal with an altered circadian rhythm (comprised of TSH bioactivity). In uremia, the pituitary receptor response to TRH is blunted causing a decrease in TSH release. The response of TSH to TRH is delayed because of the decreased clearance and the increase of half-life of TSH[14].

Experimental evidence suggests that, in uremia, the sensitivity of thyrotrophs is increased. This may account for the resetting of the central thyrostat indicating a lower level of the circulating thyroid hormones and, in turn, affect the negative feedback inhibition. In CKD, physiological compensation for low T3/T4 (with normal TSH levels) causes a reduction in protein catabolism which increases the nitrogen waste overload[11].

CHRONIC KIDNEY DISEASE AND THYROID DYSFUNCTION:

Hyperthyroidism results in intra-glomerular hypertension (increased filtration pressure) and consequent hyperfiltration. It predisposes to proteinuria, which is known to cause direct renal injury. Hyperthyroidism-induced increased mitochondrial energy metabolism along with down-regulation of superoxide dismutase

contributes to the increased free radical generation and consequent increased RAAS activity can accelerate renal fibrosis and renal injury[1].

The earliest and the most common thyroid function abnormality in CKD patients is a low T3 level (especially total T3 than free T3). This "low T3 syndrome" occurs in CKD due to several reasons. Fasting, chronic metabolic acidosis and chronic protein malnutrition affect iodothyronine deiodination, as well as protein binding of T3, reducing the peripheral conversion of T4 to T3 and its protein binding. In addition, inflammatory cytokines such as tumor necrosis factor (TNF)-α and interleukin (IL)-1 inhibit the expression of type 1 5'-deiodinase, which is responsible for peripheral conversion of T4 to T3. In addition, impaired renal handling of iodine increases serum iodine levels, causing a prolonged Wolff – Chaikoff effect. . The low T3 levels (especially total T3 and not free T3) in CKD patients have been correlated with higher levels of markers of inflammation [highly sensitive C-reactive protein (hsCRP), IL-6, etc.], malnutrition (lower prealbumin, IGF-1), increased endothelial dysfunction, poorer cardiac function, poor survival, and higher all-cause as well as cardiovascular mortality in some studies[1].

Thyroid stimulating hormone (TSH) levels are elevated in CKD. However, TSH is released in response to thyrotropin releasing hormone (TRH) in CKD patients, indicating pituitary disturbances in uremia. In addition, the circadian rhythm of TSH and its glycosylation is altered in CKD, compromising its activity. Thus, CKD patients have low T3 and normal or reduced T4 levels, and consequently elevated TSH and attendant increase in thyroid gland volume. CKD results in reduced iodide excretion, which results in increased serum inorganic iodide level and the thyroid gland iodine content and consequent thyroid gland enlargement. Structural changes in thyroid among CKD patients include an increased prevalence of goiter (especially among women), thyroid nodules, and thyroid carcinoma, compared to general population[12].

There is no increase in the incidence of autoimmune thyroid disease in CKD patients. In fact, the incidence of positive thyroglobulin and thyroid microsomal antibodies is low in CKD patients. However, autoimmune thyroid disease may occur along with other autoimmune diseases associated with CKD, such as lupus nephritis, type 1 diabetes mellitus, etc.

Figure 3: Effects of chronic kidney disease on thyroid profile[1]

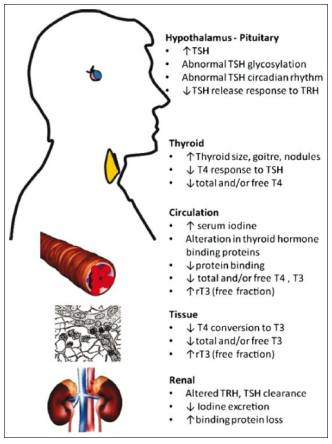
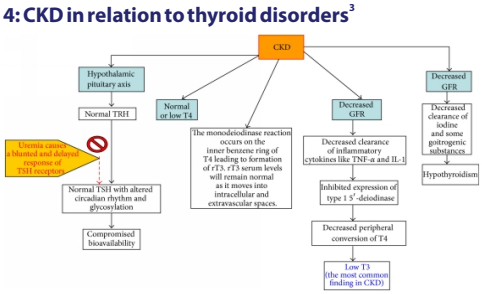


Figure 4: CKD in relation to thyroid disorders[3]



OTHER KIDNEY DISEASES ASSOCIATED WITH THYROID DYSFUNCTION:

Several glomerulonephritis may occur in association with thyroid diseases. The most commonly observed association is with membranous nephropathy, followed by IgA nephropathy, membranoproliferative glomerulonephritis, and minimal change disease. The presence of circulating immune complexes among patients with thyroid disease, the association of Hashimoto's thyroiditis and membranous nephropathy with immune complex deposition in the glomerular as well as thyroid epithelial basement membrane, and the common occurrence of thyroid and renal disease in association with other autoimmune diseases such as type 1 diabetes mellitus suggest a common autoimmune pathogenesis or an autoimmune disorder (such as lupus or vasculitis) with associated thyroid and renal disease[4].

THYROID AND RENAL CARCINOMA:

There is an increased predisposition of patients with thyroid cancer to develop renal cell carcinoma (RCC) due to genetic predisposition or treatment of disease. In addition, thyroid malignancy could metastasize to the kidney and RCC is one of the common tumors metastasizing to the thyroid[4].

CONCLUSION:

The most common changes in CKD relating to the thyroid gland are of low T3 levels and subclinical hypothyroidism. 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. Clinicians, including nephrologists, must consider the dangers of thyroid disease and its appropriate treatment in conjunction to treating CKD. Further investigation in this field will provide new insights in our understanding of the biological significance of thyroid hormone changes in patients with kidney disease.

REFERENCES:

1. Gopal Basu and Anjali Mohapatra. Interactions between thyroid disorders and kidney disease. Indian Journal of Endocrinology and Metabolism. 2012;16, 2:204-213.
2. Laura H. Mariani and Jeffrey S. Berns. The Renal Manifestations of Thyroid Disease. Journal of the American Society of Nephrology.2012;23,1 :22-26.
3. Mohamed Mohamedali, Srikanth Reddy Maddika, Anix Vyas, Viswanathan Iyer and Pramil Cheriyath. Thyroid Disorders and Chronic Kidney Disease. International Journal of Nephrology.2014; 14.
4. P Iglesias and J J Diez. Thyroid dysfunction and kidney disease. European Journal of Endocrinology.2009; 160:503-515.
5. Joan C.Lo, Glenn M.Chertow, Alan S.Go and Chi-YuanHsu. Increased prevalence of subclinical and clinical hypothyroidism in persons with chronic kidney disease. Kidney Inernational. 2005; 67,3:1047-1052.
6. Michel Chonchol, Giuseppe Lippi , Gianluca Salvagno , Giacomo Zoppini ,Michele Muggeo. Prevalence of subclinical hypothyroidism in patients with chronic kidney disease. Clinical Journal of the American Society of Nephrology. 2008; 3,5:1296-1300.
7. J. J. Carrero, A.R.Qureshi, J.Axelsson, M.I.Yilmaz, S.Rehnmark, M.R.Witt, P.Barany, O.Heimburger, M.E.Suliman, A.Alvestrand, B.Lindholm and P.Stenvinkel. Clinical and biochemical implications of low thyroid hormone levels (total and free forms) in euthyroid patients with chronic kidney disease. Journal of Internal Medicine .2007; 262,6:690-701.
8. A.I.Katz, D.S.Emmanouel and M.D.Lindheimer. Thyroid Hormone and the Kidney. Nephron.1975; 15:223-249.
9. Jan G. Den Hollander, Remi W Wulkan, Mart J.Mantel and Arie Berghout. Correlation between severity of thyroid dysfunction and renal function. Clinical Endocrinology Journal. 2005; 62, 4:423-427.
10. https://en.wikipedia.org/wiki/Chronic_kidney_disease
11. Periklis Dousdampanis, Konstantina Trigka, GeorgiosA. Vagenakisand Costas Fourtounas. The thyroid and the kidney: a complex interplay in health and disease. The International Journal of Artificial Organs.2014; 37,1:1-97.
12. Ingrid van Hoek and Sylvei Daminet. Interactions between thyroid and kidney function in pathological conditions of these organ systems: a review. General and Comparative Endocrinology. 2009; 160,3:205-15.
13. S.Khatiwada, Rajendra KC, S.Gautam,M.Lamsal and N.Baral. Thyroid dysfunction and dyslipidemia in chronic kidney disease patients. BMC Endocrine disorders.2015; 15:63-69.
14. P. Iglesias, M.A. Bajo, R.Selgas and J.J Díez.Thyroid dysfunction and kidney disease: An update. Reviews in Endocrine and Metabolic Disorders.2017; 18,1:131-144.
15. M.Ponsoye, R.Paule, V.Gueutin, G.Deray and H.Izzedine. Kidney and thyroid dysfunction. Nephrologie and Therapeutique.2012; 9,1:13-20.
16. A.Connor and JE Taylor. Renal impairment resulting from hypothyroidism..NDT Plus.2008; 1,6:440-441.
17. J.Montenegro, O.Gonzalez, R.Saracho, R.Agguire and I.Martinez. Changes in renal

function in primary hypothyroidism. American Jounal of Kidney Diseases.1996; 27,2: 195-198.
18. V.Saini, A.Yadav, M. K. Arora,S.Arora, R.Singh and J. Bhattacharjee. Correlation of creatinine with TSH levels in overt hypothyroidism - a requirement for monitoring of renal function in hypothyroid patients? Clinical Biochemistry.2012; 45,3: 212-214.
19. A.M.Abdella, B.S.Ekoon and G.A.Modawe. The impact of thyroid dysfunction on renal function tests. Saudi Journal of Kidney Diseases and Transplantation.2013; 24,1:132-134.
20. E.M.Kaptein. Thyroid Hormone Metabolism and Thyroid Diseases in Chronic Renal Failure. Endocrine reviews. 1996;17,1:45-63.