An Overview on the sign of the interaction between thyroid and kidney disease

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Abstract

Hypothyroidism is a condition in which the thyroid gland does not produce enough thyroid hormone. Hypothyroidism is associated with reduced Glomerular filtration rate and hyperthyroidism results in increased GFR as well as increased renin angiotensin aldosterone activation. Chronic Kidney disease (CKD) is characterized by a low T3 syndrome which is now considered a part of an atypical nonthyroidal illness. This review studies probable mechanistic relations between thyroid and kidney disease.

Key words: Hypothyroidism, Hyperthyroidism, Angiotensin and Aldosterone.

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Introduction

Hypothyroidism

The most common kidney disarrangements 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. These alterations may be absent in patients with central hypothyroidism due to the fact that this kind of thyroid hypofunction is often accompanied by other pituitary hormone deficiencies that might affect directly or indirectly the kidney function.[7]

Primary hypothyroidism is associated with a reduction of GFR and RPF that are normalized following levothyroxine administration. Similarly, normalization of circulating TH concentrations with replacement therapy in hypothyroid patients with chronic kidney disease (CKD) can significantly improve GFR. However, it has recently been reported that kidney function recovers slowly in hypothyroid children, and sometimes partially, after the introduction of replacement with levothyroxine. The long-term clinical implications of these findings are unknown [1].

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 disarrangements 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 [2].

Thyrotoxicosis

Thyrotoxicosis is characterized by an increase in RPF and GFR resulting in a reduction of serum creatinine levels. These changes are normalized after the control of thyroid function with appropriate treatment. Hyperthyroidism may be linked to a decrease in total body water and exchangeable K. By contrast, the amount of exchangeable Na tends to increase.[7] However, serum concentrations of Na, K, and Cl are normal. These alterations are typical of endogenous hyperthyroidism and exogenous thyrotoxicosis. However, central hyperthyroidism may not be accompanied by these changes when it is associated

with other pituitary disorders. The reduction of serum creatinine has also been reported in subclinical hyperthyroidism. However, changes in water and electrolyte metabolism have not been reported by other authors [8].

Hemodynamic changes, i.e., increase in systolic volume, heart rate, and cardiac output coupled with a reduction of peripheral vascular resistance, also participate in alteration in renal function reported in patients with hyperthyroidism. These changes are due to the increased circulating demands as a result of hypermetabolism and the need to dissipate excess heat associated with hyperthyroidism [9].

Effects of Thyroid hormone on renal physiology

TH plays an important role in growth, development, and physiology of the kidney (Figure 1). It is known that hypothyroidism reduces and hyperthyroidism increases the kidney-to-body weight ratio by a not fully understood mechanism. On the other hand, children with congenital hypothyroidism have an increased prevalence of congenital renal anomalies. These findings support an important role of TH during early embryogenesis [3].

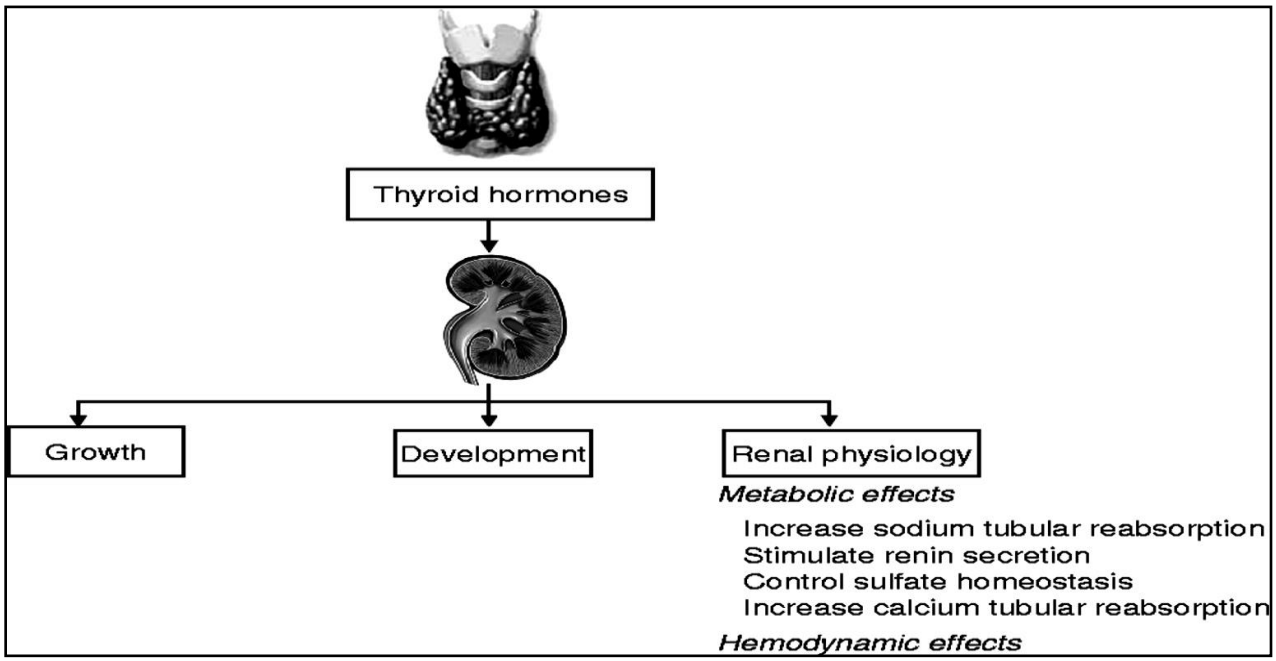

Figure 1: Effects of thyroid hormones on the kidney

Thyroid function also influences water and electrolyte balance on different compartments of the body. The kidney also plays a role on the regulation of metabolism and elimination of TH and is an important target organ for TH actions. The decrease in the activity of TH is accompanied by an inability to excrete an oral water overload. This effect is not due to an incomplete suppression of vasopressin production, or a decrease in the resorptive ability in the dilutor segment of the kidney tubule, but rather to a reduction in the glomerular filtration rate (GFR) [4].

TH have a hold upon tubular transport of sodium, via their actions on the sodium–potassium ATP pump (Na/K ATPase) and on the potassium permeability in the membrane of proximal tubules. In fact, tubular reabsorption of Na per gram of kidney tissue in rats was the lowest in thyroidectomized rats than in controls and was accompanied by a similar reduction of the specific activity of the Na-K ATPase pump. On the contrary, that activity increased when the reabsorption of Na increased in euthyroid rats treated with triiodothyronine (T_3). As it occurs with Na, the reduction of TH activity at kidney level is accompanied

by a decrease in the absorption of calcium at tubular level without affecting magnesium [5].

TH stimulates renin, released by the juxtaglomerular cells through a mechanism independent of the sensitive sodium pump and protein synthesis and influence kidney angiotensinase activity. T_3 is also involved in sulfate homeostasis through the regulation of kidney sodium-sulfate cotransporter, NaS(i)-1, a protein entailed in the control of serum sulfate levels. Finally, different studies in animals have shown that TH act on the regulation of kidney dopaminergic system [6].

Effects of thyroid dysfunction on the kidney

Thyroid dysfunction causes significant changes in kidney function (Table 1). Both hypo-thyroidism and hyperthyroidism affect renal blood flow, GFR, tubular function, electrolytes homeostasis, electrolyte pump functions, and kidney structure.

Table 1: Effects of thyroid dysfunction on the kidney

HYPOTHYROIDISM	THYROTOXICOSIS
Increased serum creatinine	Decreased serum creatinine
Decreased glomerular filtration	Increased glomerular filtration
Decreased renal plasma flow	Increased renal plasma flow
Decreased sodium reabsorption	Increased tubular reabsorption
Decreased renal ability to dilute urine	Resistance to recombinant human erythropoietin action
Hyponatremia	Decreased sodium level in serum

Kidney disease associated to thyroid dysfunction

The different types of kidney diseases can be associated with various disorders of thyroid function.

(i) Glomerular disease: Thyroid disease may be linked to different forms of glomerulonephritis. Both hypothyroidism and hyperthyroidism can coincide with different forms of glomerular disease. The more frequent form is membranous glomerulopathy associated with nephrotic syndrome (NS). Thyroid dysfunction has been reported to be associated with IgA glomerulonephritis, mesangio capillary or membranoproliferative glomerulonephritis, and minimal change glomerulonephritis [10].

Several mechanisms have been involved in these associations. Proteinuria may promote the development of primary hypothyroidism, and the immune activation of the thyroid or kidney disorders could induce the formation of immunocomplexes. The presence of immunocomplexes is common in patients with thyroid disease.

In a study performed in 171 patients with thyroid disease, the presence of immunocomplexes was detected in 26% of patients in comparison with 8% of the control subjects. This percentage increased to 33–55% in patients with an autoimmune process and was correlated with the presence of thyroid peroxidase antibodies, but not with the titer of these antibodies. Also, immunocomplexes deposits in the basement membrane of thyroid follicular epithelium and the glomeruli have been reported in patients with Hashimoto's thyroiditis and membranous glomerulopathy [11].

Therefore, several data support the autoimmune pathogenesis for this association:

i) The association of kidney and thyroid diseases of autoimmune origin.

ii) Its association with other autoimmune diseases such as type 1 diabetes.

iii) The presence of deposits of immunoglobulins and thyroglobulin in the glomeruli of some patients.

Although autoimmune thyroid disease has occasionally been reported in patients with glomerulonephritis, no causal relationship between the two disorders has been proved so far. Glomerular disease in general is associated and occasionally caused by autoimmune disease (e.g. lupus nephritis, antineutrophil cytoplasmic antibodies (ANCA) associated vasculitis) that can be associated to autoimmune thyroid disease [12]

(ii) Tubular disease: Although less frequently than glomerular disease, tubular or tubulointerstitial damage has also been reported to be associated with thyroid dysfunction. Isolated cases of hyperthyroidism have been reported in association with tubulointerstitial nephritis and uveitis, a self-limited syndrome of unknown etiology that responds to glucocorticoids. In these cases, the etiology of hyperthyroidism was not Graves' disease, but rather a destructive thyroiditis with the absence of thyroid autoimmunity, low uptake in thyroid scintigraphy, and adequate response to steroid therapy. Tubulointerstitial nephritis and hyperthyroidism has been reported to be associated in patients under treatment with rifampicin [13].

(iii) Nephrotic syndrome: NS is associated with changes in serum TH levels. Urinary losses of binding proteins, such as thyroxine binding globulin (TBG), transthyretin or pre-albumin, albumin, and TH binded to them, result in a reduction in serum total thyroxine (T_4) and, sometimes, in total T_3 levels. These hormonal changes are related both to the degree of proteinuria and to serum albumin levels [14]. However, patients often remain euthyroid, because free T_4 and T_3 levels are usually normal. This suggests that thyroid is able to compensate for hormonal urinary losses keeping the patient euthyroid. However, in patients with low thyroid reserve overt hypothyroidism can develop. Similarly, NS may increase the exogenous levothyroxine needs in patients with hypothyroidism [15].

Primary hypothyroidism linked to congenital NS (CNS) has been reported. TH urinary loss associated with the intrauterine massive proteinuria stimulates the hypothalamus–pituitary–thyroid axis increasing serum thyrotropin (TSH) concentrations. Other involved factors are malnutrition and iodine depletion. However, the main cause is TH urinary losses, since it was observed that bilateral nephrectomy followed by extra renal purification treatment reverses completely the CNS associated hypothyroidism and permits the withdrawal of hormonal treatment with levothyroxine. Some authors recommend treatment with levothyroxine supplementation in children with CNS as it facilitates their normal development [16].

(iv) Acute kidney injury: Acute kidney injury (AKI) is associated with abnormalities in thyroid function tests similar to those found in euthyroid sick syndrome (ESS). Contrary to the usual form of the ESS, patients with AKI may not exhibit an elevation or reverse (r) T_3 levels. The hypothyroidism-associated rise in serum creatinine may be of relevance in patients with thyroid carcinoma in which the withdrawal of levothyroxine treatment for total body scan preparation can lead to accumulation of drugs whose metabolism and elimination is primarily renal [17].

(v) Chronic kidney disease: CKD affects both hypothalamus–pituitary–thyroid axis and TH peripheral metabolism (Figure 2). Uremia influences the function and size of the thyroid. Uraemic patients have an increased thyroid volume compared with subjects with normal renal function and a higher prevalence of goiter, mainly in women. Also, thyroid nodules and thyroid carcinoma are more common in uraemic patients than in the general population [18].

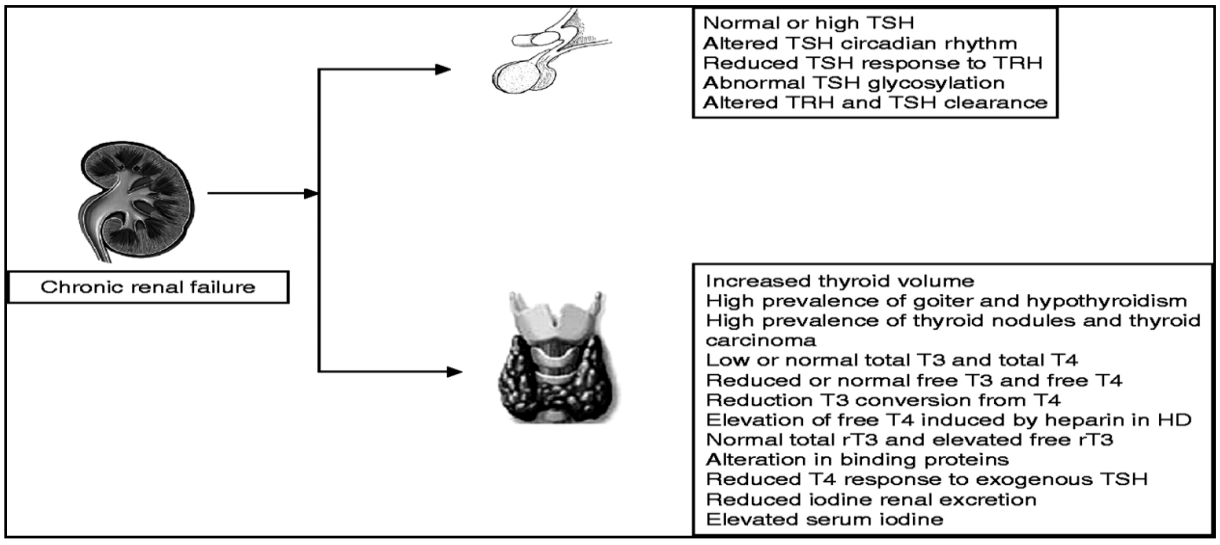

Figure 2: Effects of chronic renal failure on hypothalamus–pituitary–thyroid axis

Serum TSH concentrations are usually normal or elevated in CKD, but its response to its releasing hormone (TRH) is generally low. These findings suggest the presence of intrathyroidal and pituitary disturbances associated with uremia. Also, both TSH circadian rhythm and TSH glycosylation are altered in CKD. The latter may compromise TSH bioactivity [18].

Free and total T_3 and T_4 concentrations are usually normal or low in patients with CKD. The reduction in T_3 levels (low T_3syndrome) is the most frequently observed thyroid alteration in these patients. This reduction in T_3 concentrations has been linked to a decrease in the peripheral synthesis of T_3 from T_4. Chronic metabolic acidosis associated with the CKD may contribute in this effect. Although free and total T_4 concentrations may be normal or slightly reduced, sometimes free T_4 may be high due to the effect of heparin used in anticoagulation during hemodialysis (HD), which inhibits T_4-binding to its binding proteins [19].

As mentioned, 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.[23] The response of TSH to TRH is delayed because of the decreased clearance and the increase of half-life of TSH. Abnormal serum constituents found in uremic conditions can also displace T3 and T4 from normal protein binding sites. Normal or low levels of T4 may be due to the monodeiodinase action occurring in the inner benzene ring instead of outer ring of T4, resulting in the formation of reverse T3. Reverse T3 levels, however, are found to be normal in CKD patients because it moves from the vascular space to extra vascular and intracellular spaces. Transient increases in T4 levels are usually seen after hemodialysis.[24] This effect is mainly due to the use of heparin as an anticoagulant which inhibits T4 binding to proteins and leads to an increase in T4 levels [20].

Kidney disease in relation to thyroid disorders

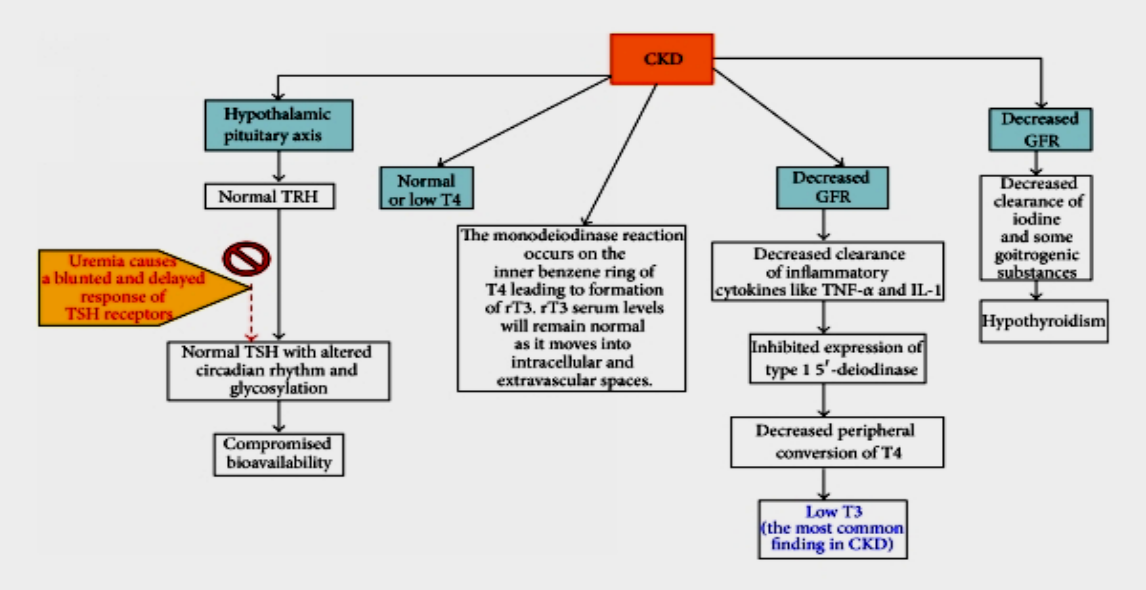

Figure 3: Kidney disease in relation to thyroid disorders

Low T3 levels in CKD may be due to the iodothyronine deiodinase (helps in T3 synthesis from T4) affected by fasting, chronic metabolic acidosis, and chronic protein malnutrition seen in CKD. Such factors influence the proteins binding to T3. Low T3 levels in CKD may also be due to the decreased peripheral (extra thyroidal) conversion from T4 to T3 due to decreased clearance of the inflammatory cytokines such as TNF-alpha and IL-1. These cytokines inhibit expression of 1 5′-deiodinase that helped convert T4 to T3. Low free T3 levels have shown to be an independent predictor of mortality in hemodialysis

patients. Low T3 levels prior to renal transplant are associated with posttransplant risks of graft loss. All clinicians are advised to check T3 levels before renal transplantation. Low T3 levels in CKD may not be able to increase TSH levels. 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 [21, 22].

REFERENCES

1. Levin A, Bakris GL, Molitch M, Smulders M, Tian J, Williams LA, et al. Prevalence of abnormal serum vitamin D, PTH, calcium, and phosphorus in patients with chronic kidney disease: results of the study to evaluate early kidney disease. Kidney Int 2007;71:31-8.
2. Andress D. Nonclassical aspects of differential vitamin D receptor activation: implications for survival in patients with chronic kidney disease. Drugs 2007;67:1999-2012.
3. P Iglesias and J J Dıez. Thyroid dysfunction and kidney disease. European Journal of Endocrinology, 2009;160:503–515.
4. Ludmilla F. Cardoso1, Lea M. Z. Maciel, Francisco J. A. de Paula. The multiple effects of thyroid disorders on bone and mineral metabolism. Arq Bras Endocrinol Metab. 2014; 58/5.
5. Q. Zhang, X. Xiao, M. Li et al., "Berberine moderates glucose metabolism through the GnRH-GLP-1 andMAPK pathways in the intestine," BMC Complementary and Alternative Medicine, 2014;14(1):188.
6. Nabeshima Y, Imura H. alpha-Klotho: a regulator that integrates calcium homeostasis. Am J Nephrol 2008;28:455-64.
7. Bahn Chair RS, Burch HB, Cooper DS, Garber JR, Greenlee MC, Klein I, et al. Hyperthyroidism and other causes of thyrotoxicosis: management guidelines of the American Thyroid Association and American Association of Clinical Endocrinologists. Thyroid. 2011;21(6):593–646.
8. Melamed ML, Eustace JA, Plantinga L, Jaar BG, Fink NE, Coresh J, et al. Changes in serum calcium, phosphate, and PTH and the risk of death in incident dialysis patients: a longitudinal study. Kidney Int 2006;70:351-7.
9. Silvia Santos Palacios, Eider Pascual-Corrales, and Juan Carlos Galofre. Management of Subclinical Hyperthyroidism. Int J Endocrinol Metab. 2012 Spring; 10(2): 490–496.
10. Salla Surya Prakasa Rao, Sweta Ramani, Manem Raveena Manem Nikitha. Cognitive functions in patients with chronic renal failure patients, Asian Pac. J. Health Sci., 2016; 3 (3):191-193.
11. Spencer CA, Hollowell JG, Kazarosyan M, Braverman LE. National Health and Nutrition Examination Survey III thyroid-stimulating hormone (TSH)-thyroperoxidase antibody relationships demonstrate that TSH upper reference limits may be skewed by occult thyroid dysfunction. J Clin Endocrinol Metab. 2007;92(11):4236–40. doi: 10.1210/jc.2007-0287.
12. Galofre JC, Davies TF. Autoimmune thyroid disease in pregnancy: a review. J Womens Health (Larchmt). 2009;18(11):1847–56.
13. Hudde T, Heinz C, Neudorf U, Hoef S, Heiligenhaus A & Steuhl KP. Tubulointerstitial nephritis and uveitis (TINU syndrome) – comorbidity and complications in four patients. Klinische Monatsblätter für Augenheilkunde 2007; 219:528–532.
14. Kaptein EM, Hoopes MT, Parise M & Massry SG. rT3 metabolism in patients with nephrotic syndrome and normal GFR compared with normal subjects. American Journal of Physiology 1991,260:E641–E650.
15. Kagiyama S, Tsuruta H, Tominaga M, Morishita K, Doi Y & Onoyama K. Minimal-change nephrotic syndrome and acute renal failure in a patient with aged onset insulin-dependent diabetes mellitus and autoimmune thyroiditis. American Journal of Nephrology 1999;19:369–372.
16. Vachvanichsanong P, Mitarnun W, Tungsinmunkong K & Dissaneewate P. Congenital and infantile nephrotic syndrome in Thai infants. Clinical Pediatrics 2005;44:169–174.
17. Kursat S, Alici T & Colak HB. A case of rhabdomyolysis induced acute renal failure secondary to statin-fibrate-derivative combination and occult hypothyroidism. Clinical Nephrology 2005;64:391–393.
18. Singh PA, Bobby Z, Selvaraj N & Vinayagamoorthi R. An evaluation of thyroid hormone status and oxidative stress in undialyzed chronic renal failure patients. Indian Journal of Physiology and Pharmacology 2006;50:279–284.
19. Kar PM, Hirani A & Allen MJ. Acute renal failure in a hypothyroid patient with rhabdomyolysis. Clinical Nephrology 2003;60:428–429.
20. Lim VS. Thyroid function in patients with chronic renal failure. American Journal of Kidney Diseases 2001;38:S80–S84.

21. Mohamed Mohamedali, Srikanth Reddy Maddika, Anix Vyas, Viswanathan Iyer, and Pramil Cheriyath, "Thyroid Disorders and Chronic Kidney Disease," International Journal of Nephrology, 2014;vol.2014, 6 pages, Article ID 520281.
22. Macchia PE, Harrison HH, Scherberg NH, Sunthornthepfvarakul T, Jaeken J, Refetoff S. Thyroid function tests and characterization of thyroxine-binding globulin in the carbohydrate-deficient glycoprotein syndrome type I. J Clin Endocrinol Metab. 1995;80(12):3744-9.
23. Gupta AK, Kothiyal P, Pandey S. Evaluation of antiurolithiatic potential of *Kigelia africana* fruits in albino rats. FABAD J Pharm Sci 2011;36:197-205.
24. Gupta AK, Kothiyal P. *In-vitro* antiurolithiatic activity of *Kigelia africana* fruit extracts. Indian J Pharm Bio Res 2015;3:77-81.

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