KIDNEYS AND THYROID GLAND: INTERRELATION IN HEALTH AND DISEASE

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ABSTRACT

Chronic kidney disease (CKD) is a global health threat associated with an alarming increase in morbidity and mortality. There are many mechanisms explaining the link between thyroid and kidney disease. Thyroid hormones have pre-renal and intrinsic renal effects by which they increase the renal blood flow and glomerular filtration rate (GFR). Hypothyroidism is associated with reduced GFR and hyperthyroidism results in increased GFR as well as increased renin-angiotensin-aldosterone activation. CKD patients also have increased incidence of primary and sub-clinical hypothyroidism. The physiological benefits of a hypothyroid state in CKD, and the risk of CKD progression with hyperthyroidism emphasize on a conservative approach in the treatment of thyroid hormone abnormalities in CKD. Thyroid dysfunction is also associated with glomerulonephritis often by a common autoimmune etiology. Several drugs could affect both thyroid and kidney functions. All of these aspects are covered in the present review. The variable association of low T3 to inflammation, endothelial dysfunction, and poor survival in CKD and transplant patients is of importance. A detailed knowledge of these interactions is important for both the nephrologists and endocrinologists for optimal diagnosis and management of the patient.


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INTRODUCTION

Thyroid hormones are necessary for growth and development of the kidney and for the maintenance of water and electrolyte homeostasis [1]. On other hand, kidney is involved in the metabolism and elimination of thyroid hormones. From a clinical practice viewpoint, it should be mentioned that both hypothyroidism and hyperthyroidism are accompanied by remarkable alteration in the metabolism of water and electrolytes, as well as in cardiovascular function [2]. Moreover, the decline of kidney function is accompanied by changes in the thyroid hormone synthesis, secretion, metabolism and elimination [3]. Thyroid acquires special characteristics in patients with advanced kidney disease [4]. On the other hand, the different treatments used in the management of patients with kidney and thyroid diseases may be accompanied by changes or adverse events that affect thyroid and kidney function respectively.

Chronic diseases have become a major public health problem. Chronic diseases are a leading cause of morbidity and mortality in India and other low- and middle-income countries. They account for 60% of all deaths worldwide. In India, the projected numbers of deaths due to chronic disease was around 5.21 million in 2008 and is expected to rise to 7.63 million by 2020 (66.67% of all deaths) [5].

Chronic kidney disease (CKD) encompasses a spectrum of different pathophysiology processes associated with abnormal kidney function, and a progressive decline in glomerular filtration rate (GFR)[6,8]. CKD is a clinical syndrome due to irreversible kidney dysfunction leading to excretory, metabolic and synthetic failure culminating into accumulation of non-protein nitrogenous substances and presenting with various clinical manifestation [7].

The frequency of chronic kidney disease (CKD) is increasing worldwide as does the prevalence of end-stage kidney disease (ESKD). The most common, but not only, causes of CKD are hypertension and diabetes. The presence of CKD is associated with a large increase in cardiovascular (CV) risk. Moreover, CV risk increases proportionally as e-GFR falls below 60 ml/min. Lastly, death from CV causes is eight-fold higher in CKD, much higher than death from cancer. Consequently, the identification and reduction of CKD has become a vital public health priority.

The reported prevalence of CKD stages 1-4 in the most recent NHANES (National Health and Nutrition Examination Survey) between 1999 and 2006 was 26 million (13%) out of approximately 200 million United states residents aged 20 years and older. Of these, 65.3% had CKD stages 3 or 4. The most recent report of the United States Renal Data System estimates that nearly one-half million patients in the United States were treated for ESRD in the year 2004, and by 2010 this figure is expected to increase by approximately 40%. The elderly are a growing segment of the population and at increased risk for renal disease. Additionally, males and African-Americans with pre-existing hypertension or diabetes and CKD are also at much higher risk for ESRD. These observations have also been confirmed throughout the developed world: Europe, Asia, Australia as well as in developing regions such as China, India and Africa [9].

The biochemical interrelationships between thyroid and kidneys and their alterations in disease are the subject of the present review.

CARDIOVASCULAR DISEASE, MORTALITY AND LOW T₃ IN CKD

Tri-iodothyronine (T₃) is a key signal in myocardial cells [10]. The causal role of T₃ deficiency in heart failure is supported by a short-term clinical trial where synthetic L-T₃ replacement therapy elicited a clear-cut improvement in the neurohumoral profile and in left ventricle (LV) performance in these patients [11]. T₃ should be seen as a critical regulator of cell biology impinging also on cell replication, oxidative phosphorylation, mitochondrial gene transcription, and the generation of various intracellular secondary messengers. As alluded to before, lowT₃ in nonthyroidal diseases, such as kidney failure, was interpreted as a protective adaptation to protein and energy wasting. However, persistently low T₃ levels may eventually become a maladaptive response [12], because such an alteration entails a negative prognosis in several severe diseases including diseases treated in intensive care units, liver cirrhosis, pulmonary and cardiac disease, and kidney failure.

Inflammation plays a central role in the morbidity of dialysis patients, and inflammation markers have been consistently associated with atherosclerosis, LV dysfunction, and LV hypertrophy in this population. The coherent association of low T₃ with high levels of inflammation markers as well as with mortality and cardiomyopathy suggests that subnormal T₃ may be a relevant factor in the chain of events whereby inflammation perpetuates engenders a high risk for death and cardiovascular disease in this population [13].

EFFECTS OF THYROID DYSFUNCTION ON THE KIDNEYS

Thyroid dysfunction affects renal blood flow (RBF), Glomerular filtration rate GFR, tubular function, electrolyte homeostasis, and kidney structure. The various effects of hypothyroidism and hyperthyroidism on renal function have been summarized in Fig:1. The effects on renal function tests are listed in Table:1.
Fig.1. Thyroid dysfunction and the kidneys.

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

<table>
<thead>
<tr>
<th>Tests</th>
<th>Hypothyroidism</th>
<th>Hyperthyroidism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Creatinine</td>
<td>Increased</td>
<td>Decreased</td>
</tr>
<tr>
<td>Serum cystatin C</td>
<td>Decreased</td>
<td>Increased</td>
</tr>
<tr>
<td>Urinary NGAL</td>
<td>Unchanged</td>
<td>Unchanged</td>
</tr>
<tr>
<td>24-hour urine protein</td>
<td>Increased</td>
<td>Increased</td>
</tr>
<tr>
<td>Water load excretion</td>
<td>Decreased</td>
<td>Increased</td>
</tr>
<tr>
<td>Electrolytes, Neutrophil gelatinase associated lipocalin</td>
<td>Hyponatremia</td>
<td>None</td>
</tr>
</tbody>
</table>

HYPERTHYROIDISM

Hyperthyroidism results in increased RBF and GFR [14]. The effect of thyroid hormones on RBF and GFR occurs at multiple levels. Among the pre-renal factors, thyroid hormones increase the cardiac output by positive chronotropic [15] and inotropic effects[16] as well as a reduction in systemic vascular resistance [17]. This indirectly contributes to an increase in RBF. There is an increased endothelial production of nitric oxide (NO) in the renal cortex and medulla by induction of nitric oxide synthase (NOS) [18], directly by the thyroid hormones and indirectly by high arterial pressure related endothelial shear stress [19]. This is accompanied by a reduction in renal vasoconstrictor endothelin[20]. Thus, an increased intrarenal vasodilatation and decreased vasoconstriction ensues, contributing to a net increase in RBF, by about 18–25% [21]. This improvement in GFR is not solely due to an increased RBF. The activation of renin – angiotensin – aldosterone system (RAAS) also contributes to the increase in GFR. Thyroid hormones stimulate the RAAS in a multifactorial manner. In hyperthyroidism, there is increased β-adrenergic activity, accompanied by increased density of β-adrenergic receptors in the renal cortex, resulting in increased stimulation of RAAS [22]. T3 increases the renin gene expression. Thyroid hormones increase the plasma renin, angiotensin II, and serum angiotensin converting enzyme levels. In addition, there is an increase in angiotensinogen synthesis by liver and increased density of angiotensin receptors [23]. Thus, there is a net increase in the RAAS activity. This results in afferent arteriolar vasodilatation and efferent arteriolar vasoconstriction and a consequent increased filtration pressure. This adds to the magnitude of increase in GFR over and above that contributed by an increase in RBF. Efferent arteriolar vasoconstriction could result in hypoperfusion of the Proximal Convoluted Tubules (PCT) and consequent avid sodium and chloride reabsorption in PCT. In addition, there is an increased activity of the basolateral NA/K ATPase[24], apical Na – H exchanger (NHE)[25], and the Na – Pi co-transporter[26]. Activation of these transporters increases the proximal sodium reabsorption. There is a simultaneous increase in the tubular mass, renal mass, and tubular reabsorptive capacity in hyperthyroidism [27]. The increase in basolateral sodium concentration feeds the basolateral sodium calcium exchanger [28]. The avid Cl reabsorption along with its
transport through the basolateral chloride channel indirectly increases the calcium reabsorption, especially at the loop of Henle. Thus, there is a decreased Cl delivery to distal nephron. This is sensed by the macula densa which in turn increases the RAAS activity. Hyperthyroidism results in an increase in the sensitivity of macula densa, and therefore further RAAS activation [29]. On treating the hyperthyroidism, these effects are reversed and the GFR returns to normal [30].

Serum creatinine, an inverse marker of GFR, is significantly decreased in hyperthyroid patients, not only due to an increase in GFR but also due to the reduction due to overall muscle mass[31]. Cystatin C, a cysteine protease inhibitor constitutively secreted by all nucleated cells, is a new marker of renal function and indicator of future cardiovascular risk. In hyperthyroidism, increased cell metabolism and production of cystatin C results in increase in serum cystatin C levels despite an increase in GFR. Serum cystatin C levels do not correlate well with GFR in hyperthyroidism. Treatment of hyperthyroidism results in a rebound increase in serum creatinine and decrease in serum cystatin C levels [32]. Urinary neutrophil gelatinase associated lipocalin (NGAL), a promising biomarker of reduced renal function, seems unchanged by the thyroid status. The 24-hour urine protein increase in hyperthyroidism is probably related to glomerular hyperfiltration[33], which resolves on treating hyperthyroidism. Urinary N-acetyl-β-D-glucosaminidase (NAG) is increased in hyperthyroidism consequent to glomerular basement membrane disruption and tubular damage due to hyperfiltration, hypertrophy, and hyperplasia [34]. There is a decreased ability to concentrate urine, probably due to increased RBF and osmotic diuresis, rather than vasopressin insensitivity [35].

Hyperthyroidism is associated with a decrease in total body water and exchangeable potassium but not sodium. However, for most part, the serum concentrations of sodium and potassium remain normal. Occasionally, hyperthyroidism is associated with hypokalemia (thyrotoxic hypokalemic periodic paralysis of channelopathies) due to genetic mutation in either L-type calcium channel α1-subunit or potassium inward rectifier 2.6.

**HYPOTHYROIDISM**

The effects of hypothyroidism on the kidney are usually opposite to the effects of hyperthyroidism. The RBF is reduced in hypothyroidism by decreased cardiac output (negative chronotropic and inotropic effects)[36], increased peripheral vascular resistance[37], intrarenal vasoconstriction[38], reduced renal response to vasodilators[39], and a reduced expression of renal vasodilators such as vascular endothelial growth factor (VEGF) and insulin like growth factor-1 (IGF-1)[40]. In addition, pathologic changes in the glomerular structure in hypothyroidism, such as glomerular basement membrane thickening and mesangial matrix expansion, may also contribute to reduce RBF [41]. The GFR is reversibly reduced (by about 40%) in more than 55% of adults with hypothyroidism[42] due to several reasons (Table 2) [43,44,45,46].

<table>
<thead>
<tr>
<th>Table 2: Factors causing loss of GFR in hypothyroidism</th>
</tr>
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<tbody>
<tr>
<td>- Decreased sensitivity to β-adrenergic stimulus and decreased renin release, along with decreased</td>
</tr>
<tr>
<td>- Angiotensin II and impaired RAAS activity.</td>
</tr>
<tr>
<td>- Structural constraint imposed by limited glomerular surface area for filtration due to renal parenchymal growth retardation in hypothyroidism.</td>
</tr>
<tr>
<td>- Reduced proximal tubular absorption of sodium chloride, and water.</td>
</tr>
<tr>
<td>- 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.</td>
</tr>
</tbody>
</table>

The tubular transport capacity is reduced and the activity of Na/K ATPase is reduced initially in the proximal tubules and later in almost all segments of the nephrons [47]. In addition, the NHE activity is also reduced in hypothyroidism [48]. Thus, 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 [49]. However, hypothyroidism causes a reversible increase in vasopressin (antidiuretic hormone or ADH) sensitivity of the collecting ducts, thus increasing free water reabsorption. The increased fluid retention, however, is unable to maximally suppress ADH in hypothyroidism [50]. The resistance of pituitary response to increased fluid retention leads to continued ADH activity and further free water retention. Hypothyroidism results in low cardiac output which triggers the carotid baroreceptors and consequently increases the non-osmotic ADH secretion [51]. In some patients, the urine sodium is not as low as would be expected with reduced cardiac output. In these patients, it is possible that the ADH secretion could be considered as inappropriate. The reduced GFR, reduced sodium reabsorption, and relatively increased ADH secretion and renal ADH supersensitivity mediated impaired free water clearance, all contribute to hyponatremia in hypothyroidism [52]. Hyponatremia is twice as common among hypothyroid patients with raised serum creatinine as among those with normal serum creatinine. There is a reversible reduction in the kidney to body weight ratio in hypothyroidism, where the renal mass almost doubles with treatment. Hypothyroidism results in a reversible elevation in serum creatinine due to the reduction in GFR as well as possible myopathy and rhabdomyolysis. There is a reduction in serum cystatin C levels in hypothyroidism due to reduced production, consequent to reduced cellular metabolism [53]. Both these changes are reversible with treatment of hypothyroidism. An increased glomerular capillary permeability to proteins and the consequent proteinuria often precedes the reduction in GFR in hypothyroidism [54].
THYROID HORMONE METABOLISM AND THE KIDNEY

Due to suboptimal deiodinase activity, tissue and circulating levels of the active form of the thyroid hormone, $T_3$, are low in CKD [55]. Because of reduced renal excretion, inorganic iodide generated by residual deiodinase activity accumulates in stage 4 and 5 CKD, which in turn dampens thyroid hormone synthesis. On the other hand, accumulation of toxic uremic solutes alters the central (hypothalamic) control of the pituitary gland, and the TSH response to thyrotropin-releasing hormone is subnormal in patients with kidney failure [56]. In contrast, the thyroid–pituitary feedback loop seems to remain intact, because steady-state plasma TSH remains substantially normal and TSH undergoes the expected rise after thyroidectomy in such patients [57]. Central effects apart, toxic uremic solutes such as urea, creatinine, indoles, and phenols inhibit protein binding of T4 [58]. Furthermore, studies in the last decade showed that systemic inflammation [59] as well as metabolic acidosis [60] may alter thyroid function in CKD patients. Low $T_3$ is the most frequent alteration of the thyroid hormone profile observed in CKD. This alteration has long been considered an innocent metabolic adaptation to chronic illness. However, low $T_3$ associates with endothelial dysfunction, a harbinger of atherosclerosis, in stage 3 and 4 CKD patients [61], as well as with cardiomyopathy [62] and with a high risk of death in stage 5 CKD patients [63].

THYROID DYSFUNCTION IN DIALYSIS AND KIDNEY TRANSPLANTATION

Patients on hemodialysis (HD) due to CKD have reduced thyroid hormone levels and elevated TSH. The minor increases in TSH levels (5 – 20 mU/l), observed in nearly 20% of uremic patients, are usually not considered to be reflecting “hypothyroidism” in this select group of patients. Though the total $T_4$ levels are low, heparin inhibits T4 binding to protein, thereby increasing free $T_4$ fraction in CKD patients after heparin dialysis [64]. Among the CKD patients on HD, there is a compensatory influence on cellular transport of thyroid hormones, which helps maintain the euthyroid state despite low serum thyroid hormone levels [65]. For all these reasons, despite low serum thyroid hormone profile, thyroid hormone supplementation should not be initiated without substantial elevation in TSH level and careful consideration. Among patients on peritoneal dialysis (PD), there is a significant increase in prevalence of hypothyroidism (particularly subclinical) and low $T_3$ levels [66]. Thyroxine binding globulin (TBG), $T_4$, and $T_3$ are lost in the PD effluent. Despite continuous and substantial protein loss, TBG levels are normal. The $T_4$ and $T_3$ losses are minor (10% and 1%, respectively) and easily compensated for. Thus, thyroid hormone replacement is not necessary in CKD patients on PD.

Kidney transplantation reverses the CKD syndrome and thus has an effect of CKD-mediated thyroid profile abnormalities. The low $T_3$ and $T_4$ levels recover after transplantation, although gradually, over the first 3–4 months. During the initial few months after transplantation, kidney transplant patients predominantly exhibit a reduction in $T_4$ levels lower than the pre-transplant level, before it gradually rises back to normal [67]. In general, post-transplant thyroid volume and free $T_3$ levels correlate well with graft function [68]. Pre-transplant low $T_3$ levels are associated with future risk of graft loss [69]. But therapy with $T_3$ supplementation does not improve graft survival, negating the possibility of a causal association [70]. Thus, there is no need to supplement thyroid hormones for the low $T_3$ levels noted in the first few months of renal transplantation. Thyroid carcinoma is the fifth most common malignancy among kidney transplant patients [71].

OTHER KIDNEY DISEASES ASSOCIATED WITH THYROID DYSFUNCTION

Several glomerulonephritides may occur in association with thyroid diseases. The most commonly observed association is with membranous nephropathy [72], followed by IgA nephropathy [73], membranoproliferative glomerulonephritis [74], and minimal change disease [75]. There are several mechanisms for these associations. The presence of circulating immune complexes among patients with thyroid disease [76], the association of Hashimoto’s thyroiditis and membranous nephropathy with immune complex deposition in the glomerular as well as thyroid epithelial basement membrane [77], and the common occurrence of thyroid and renal disease in association with other autoimmune diseases such as type 1 diabetes mellitus [78] suggest a common autoimmune

Table 3: Drugs in thyroid and renal diseases

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Adverse Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thionamides (methimazole,</td>
<td>Hyperthyroidism</td>
<td>Hypothyroidism, glomerulonephritis, vasculitis, lupus nephritis</td>
</tr>
<tr>
<td>carbamazole, propylthiouracil)</td>
<td></td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>RCC</td>
<td>Hypothyroidism, nephrogenic diabetes insipidus, CKD</td>
</tr>
<tr>
<td>Lithium</td>
<td>Manic depressive psychosis</td>
<td>Hypothyroidism, acute kidney damage</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>Cardiac arrhythmias</td>
<td>Hyperthyroidism</td>
</tr>
<tr>
<td>Interferone-α</td>
<td>Hepatitis B or C</td>
<td>Subacute thyroiditis and transient thyrotoxicosis</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>RCC</td>
<td>Hyperthyroidism, tubulointerstitial nephritis</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>Tuberculosis</td>
<td>Autoimmune thyroid disease</td>
</tr>
<tr>
<td>Alemtuzumab</td>
<td>Renal transplantation</td>
<td>Needs dose reduction in CKD and in patients an peritoneal dialysis</td>
</tr>
<tr>
<td>$^{131}$I treatment</td>
<td>Used in therapy of Graves’ disease and thyroid carcinoma</td>
<td></td>
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pathogenesis or an autoimmune disorder (such as lupus or vasculitis) with associated thyroid and renal disease. Hypothyroidism could result in obstructive sleep apnea which is associated independently with minimal change disease. Proteinuria, especially in nephrotic syndrome, often results in urinary loss of thyroid hormones bound to the various binding proteins such as TBG, albumin, prealbumin, and transthyretin [79]. This results in a reduction in the serum total thyroid hormone levels. Thyroid compensates for this by increasing the free fraction of the hormones and maintaining euthyroid state. However, patients with low thyroid reserve may develop hypothyroidism consequent to this urinary loss. In patients on supplemental thyroxine, proteinuria can increase the dose requirement to maintain euthyroid state [80]. Primary hypothyroidism has also been described in congenital nephrotic syndrome, with urinary loss of thyroid hormones resulting in increased TSH level in utero [81].

In addition to the glomerulonephritides mentioned above, isolated cases of hyperthyroidism have been associated with tubulointerstitial nephritis and uveitis (TINU) syndrome [82]. The disease responds well to steroid therapy. Patients with acute kidney injury may develop euthyroid sick syndrome, but without elevation of reverse T₃ levels [83]. Hypothyroidism can result in rhabdomyolysis related acute kidney injury [84].

THYROID AND RENAL MALIGNANCY

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. While clear cell carcinoma of thyroid, morphologically resembling the RCC, is described, some RCC may morphologically resemble thyroid follicular carcinoma. Thyroid malignancies expressing erythropoietin (EPO) receptors have favorable prognosis, while RCC expressing aberrant thyroid hormone receptors may contribute to carcinogenesis [85].

DRUGS IN THYROID AND RENAL DISEASE

Drugs used in thyroid or kidney disease may have adverse effects on the other organ’s functions as shown in Table 3.

CONCLUSIONS

Kidney is one of the most rapidly renewing tissues in our body and it response promptly to injury [86]. There are multiple interactions between kidney and thyroid functions which may be altered in the disease states involving the counterpart. There are not only functional alterations but also structural correlates of these interactions. TSH elevations are common in CKD and do not always reflect hypothyroidism. In addition, therapeutic measures of CKD such as HD, PD, and kidney transplantation have profound effects on thyroid function. Drugs used in thyroid dysfunction may result in renal dysfunction or require dose reduction in CKD. The variable association of low T₃ with inflammation, endothelial dysfunction, and poor survival in CKD and transplant patients is of importance. The bottom line is that, a detailed knowledge of these interactions is important for both the nephrologists and endocrinologists for optimal diagnosis and management of the patient.

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