Review Article

Interactions between thyroid disorders and kidney disease

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ABSTRACT

There are several interactions between thyroid and kidney functions in each other organ's disease states. Thyroid hormones affect renal development and physiology. Thyroid hormones have pre-renal and intrinsic renal effects by which they increase the renal blood flow and the glomerular filtration rate (GFR). Hypothyroidism is associated with reduced GFR 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. CKD patients also have increased incidence of primary hypothyroidism and subclinical 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. There are few described interactions between thyroid and renal malignancies. A detailed knowledge of all these interactions is important for both the nephrologists and endocrinologists for optimal management of the patient.

Key words: Chronic kidney disease, hyperthyroidism, hypothyroidism, kidney disease, renal function, thyroid disorder

Introduction

The interplay between thyroid and the kidney in each other's functions is known for many years.[1] Thyroid dysfunction affects renal physiology and development, whereas kidney disease could result in thyroid dysfunction. Disorders of the thyroid and kidney may co-exist with common etiological factors. In addition, treatment strategies of one disease may affect those of the other organ. This review focuses on the important and clinically relevant interactions between thyroid function and renal function, which are essential for the clinician to optimally manage the patient.

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Materials and Methods

A search for articles using PubMed search with terms thyroid, hypothyroidism, hyperthyroidism, and renal function, glomerular filtration rate, glomerulonephritis, chronic kidney disease, hemodialysis, peritoneal dialysis, kidney transplantation, and renal carcinoma was performed. The most relevant and current articles were selected, retrieved in their original form or abstracts, as available. The data were collated and analyzed to represent information from the best and current available form of evidence in the particular area. Several classical papers describing certain earlier developments were also cited.

Effects of Thyroid Hormones on Renal Development

Thyroid hormones influence protein synthesis and cell growth. Studies in neonatal rats have demonstrated the accelerating effect of thyroid hormones on renal development.[2] Thyroid hormone status affects the functioning renal mass (measured as the kidney to body

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mass ratio), with hypothyroidism reducing this ratio and hyperthyroidism increasing it.[3] However, severe hyperthyroidism results in protein breakdown and eventual renal atrophy. In addition, children with congenital hypothyroidism have a high incidence of congenital renal anomalies.[4] 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).[5] There is an increase in the activity of the Na – P co-transporter (NaPi),[6] Na – H exchanger (NHE),[7] as well as the Na/K ATPase[8] in the PCT. Thus, thyroid hormones play an important role in renal development and early renal function.

Effects of Thyroid Hormones on Renal Physiology

Thyroid hormones affect renal function by both pre-renal and direct renal effects.

1. Pre-renal effects are mediated by the influence of thyroid hormones on the cardiovascular system and the renal blood flow (RBF).
2. The direct renal effects are mediated by the effect of thyroid hormones on
   a. glomerular filtration rate (GFR),
   b. tubular secretory and re-absorptive processes, as well as the
   c. hormonal influences on renal tubular physiology.

Thyroid hormones affect renal clearance of water load by their effects on the GFR.[9] 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[10] and tubular potassium permeability.[11] Tubular reabsorption of calcium is affected in a similar manner, but not that of magnesium.[12] Thyroid hormones also regulate the adrenergic receptors and dopaminergic activation of the renal tubular cells.[13] They have been shown to affect the renin – angiotensin – aldosterone axis by adrenergic regulation,[14] renin release,[15] as well as influencing the angiotensinase activity.[16]

Effects of Thyroid Dysfunction on the Kidney

Thyroid dysfunction affects RBF, GFR, tubular function, electrolyte homeostasis, and kidney structure. The various effects of hypothyroidism and hyperthyroidism on renal function have been summarized in Figure 1. The effects on renal function tests are listed in Table 1.

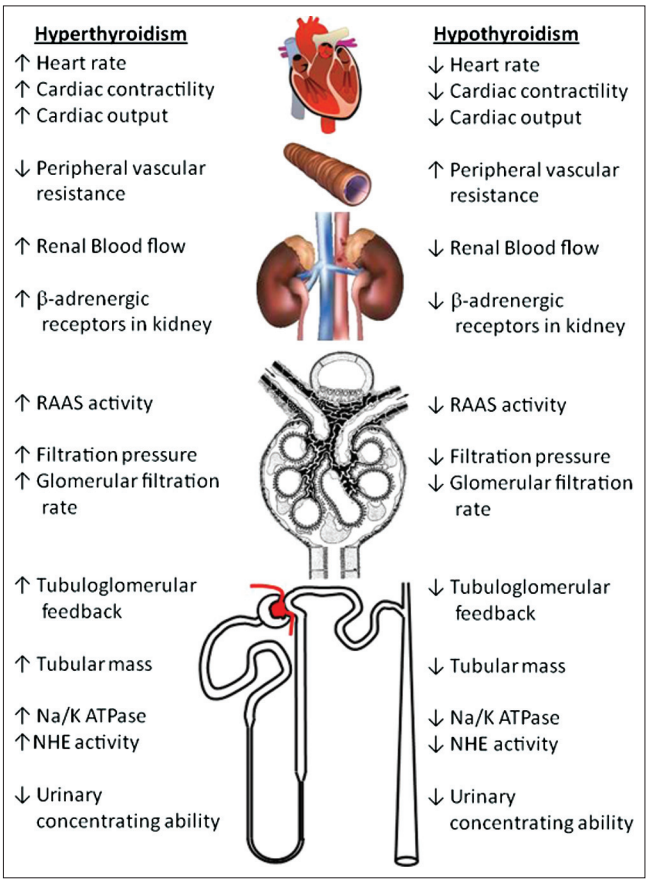

Figure 1: Effects of hyperthyroidism and hypothyroidism on renal physiology and function

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

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

Hyperthyroidism and Renal Function

Hyperthyroidism results in increased RBF and GFR.[17] 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[18] and inotropic effects[19] as well as a reduction in systemic vascular resistance.[20] 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),[21] directly by the thyroid hormones and indirectly by high arterial pressure related endothelial shear stress.[22] This

is accompanied by a reduction in renal vasoconstrictor endothelin.[23] Thus, an increased intrarenal vasodilatation and decreased vasoconstriction ensues, contributing to a net increase in RBF.

The GFR increases by about 18–25% among hyperthyroid patients.[17] 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.[24] 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.[25] 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 PCT and consequent avid sodium and chloride reabsorption in PCT. In addition, there is an increased activity of the basolateral NA/K ATPase,[5] apical Na – H exchanger (NHE),[7] and the Na – Pi co-transporter.[6] 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.[26] The increase in basolateral sodium concentration feeds the basolateral sodium calcium exchanger.[27] 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.[28] On treating the hyperthyroidism, these effects are reversed and the GFR returns to normal.[17]

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 in overall muscle mass.[29] 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.[30] 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.[30] 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,[3] 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.[31] There is a decreased ability to concentrate urine, probably due to increased RBF and osmotic diuresis, rather than vasopressin insensitivity.[32] 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.[33]

Hypothyroidism and Renal Function

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),[34] increased peripheral vascular resistance,[35] intrarenal vasoconstriction,[36] reduced renal response to vasodilators,[37] and a reduced expression of renal vasodilators such as vascular endothelial growth factor (VEGF) and insulin like growth factor-1 (IGF-1).[38] In addition, pathologic changes in the glomerular structure in hypothyroidism, such as glomerular basement membrane thickening and mesangial matrix expansion, may also contribute to reduced RBF.[39]

The GFR is reversibly reduced (by about 40%) in more than 55% of adults with hypothyroidism[40] due to several reasons. There is decreased sensitivity to β-adrenergic stimulus and decreased renin release,[3] along with decreased angiotensin II and impaired RAAS activity, resulting in loss of GFR.[25] There is a structural constraint imposed by limited glomerular surface area for filtration due to renal parenchymal growth retardation in hypothyroidism.[39] There is a reduced proximal tubular absorption of sodium,

chloride, and water.[41] 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.

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 nephron.[42] In addition, the NHE activity is also reduced in hypothyroidism.[43] 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.[44] 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.[45] 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.[46] 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.[40] 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.[30] Both these changes are reversible with treatment of hypothyroidism. Hypothyroidism also results in increased glomerular capillary permeability to proteins.[47] The consequent proteinuria often precedes the reduction in GFR in hypothyroidism.[48]

Chronic Kidney Disease and Thyroid Dysfunction

Hyperthyroidism can result in/accelerate chronic kidney disease (CKD) by several mechanisms. Firstly, hyperthyroidism results in intra-glomerular hypertension (increased filtration pressure) and consequent hyperfiltration. Secondly, hyperthyroidism predisposes to proteinuria, which is known to cause direct renal injury. Thirdly, hyperthyroidism-induced increased mitochondrial energy metabolism along with down-regulation of superoxide dismutase contributes to the increased free radical generation and consequent renal injury.[49] Oxidative stress also contributes to hypertension in hyperthyroidism, which contributes to CKD progression.[3] The increased RAAS activity can accelerate renal fibrosis. In addition, hyperthyroidism contributes to anemia in CKD patients and is considered one of the causes of resistance to recombinant human erythropoietin (EPO).[50] For the abovementioned reasons, hypothyroidism does not contribute to progression of CKD except by the mild to moderate reduction in GFR. Treatment of hypothyroidism can result in improvement of GFR in CKD patients.[51]

Primary hypothyroidism (non-autoimmune) is commonly observed in CKD patients. Especially, the prevalence of subclinical hypothyroidism increases consistently with decline in GFR.[52] The earliest and the most common thyroid function abnormality in CKD patients is a low T3 level (especially total T3 than free T3).[53] 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.[54] In addition, impaired renal handling of iodine increases serum iodine levels, causing a prolonged Wolff – Chaikoff effect.[55] The clinical importance of this low T3 syndrome is controversial. 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.[54,56] Some of these studies were underpowered to detect these associations or did not exclude confounders appropriately.[57] In some other studies, the low free T3 and not the total T3 level is associated with increased mortality.[58] However,

recent studies have demonstrated that this association is not invariable, and the free T3 levels may not be associated with long-term mortality in CKD and dialysis patients.[59]

Subsequent studies also demonstrated a low T4 level in many CKD patients. However, the free T4 levels vary from being low to normal in CKD. This is primarily because of an impaired protein binding of T4 in CKD. The thyroid profile is similar to that observed in several non-thyroidal illnesses (NTIs) such as severe infections, heart failure, malignancies, and in several hospitalized patients without renal disease. This led to the consideration of a "sick euthyroid state" in CKD, which is now called "non-thyroidal illness." However, unlike other NTI states, there is no increase in total rT3 levels in CKD.[60] This is due to an increased redistribution of rT3 into extravascular and intracellular spaces. In some patients, due to an impaired renal clearance, free rT3 levels may be mildly elevated. Another difference from other NTIs is that the 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.[61] 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.[62-64] These mechanisms are probably reflective of the physiological adaptation of the body to CKD to reduce the protein nitrogen turnover, reduce the protein catabolism and nitrogenous waste load. The reduced T3 levels and associated complications without increase in rT3, the reduced free T4 levels along with an elevated TSH, and hyporesponsiveness of TSH to TRH question the "euthyroid" state and raise the possibility of benefit from thyroid supplementation CKD. However, three decades of research in this area have not been able to clarify the need for thyroid hormone replacement in CKD. Attempts at T3 replacement have often resulted in negative nitrogen balance by increased muscle catabolism, implying the prudence in not correcting the low T3 state in CKD. Though it is clear that hypothyroidism would threaten the patient's well-being, it is not clear as to what level of thyroid dysfunction forms the threshold necessary for treatment by thyroxine replacement in CKD. In general, mild elevations of TSH (less than 20 IU/ml) with or without low T3/T4generally do not warrant thyroid hormone supplementation. One has to consider the dangers of hyperthyroidism as well as the teleological benefits of a hypothyroid state in CKD and the lack of clearly evident benefits of thyroid hormone replacement in the literature before deciding on therapy. A clinical decision of the treating nephrologists and endocrinologists should be made on an individual patient basis, after carefully considering the clinical features, possible hypothyroid manifestations, putative benefits, and possible risks of thyroid hormone therapy or the lack of it.

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.[65]

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. When elevated TSH is detected in association with other autoimmune disease, it is important to screen for antithyroid antibodies. Management strategy for autoimmune thyroid disease remains unaltered by the presence of CKD.

The various effects of CKD on thyroid profile are depicted in Figure 2.

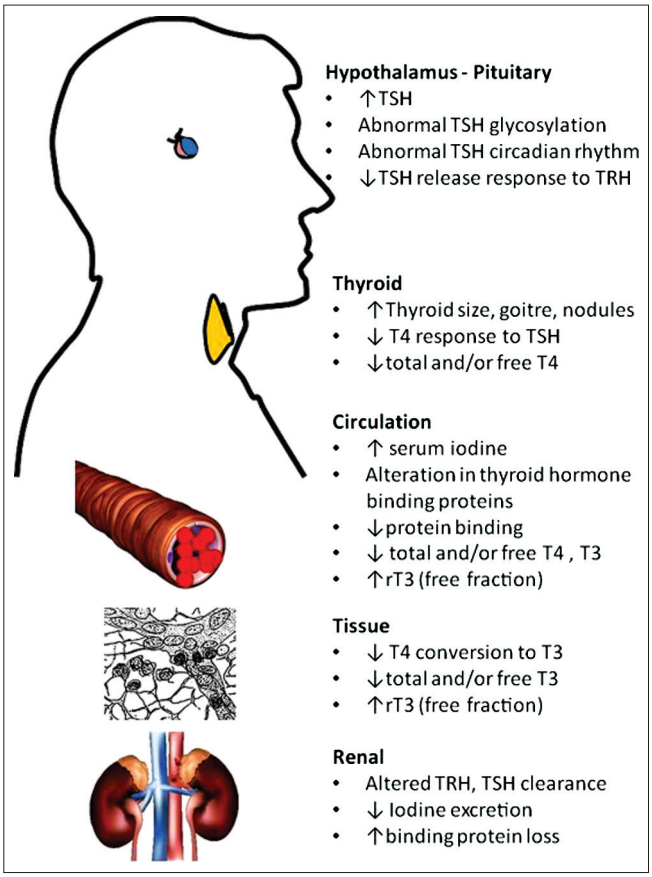

Figure 2: Effects of chronic kidney disease on thyroid profile

Thyroid Dysfunction in Dialysis and Kidney Transplantation

Patients on hemodialysis (HD) due to CKD have low thyroid hormone levels and elevated TSH. The minor increases in TSH levels (5 – 20 mU/l), observed in about 20% of uremic patients, are usually not considered to be reflecting "hypothyroidism" in this select group of patients. Though the total T4 levels are low, heparin inhibits T4 binding to protein, thereby increasing free T4 fraction in CKD patients after heparin dialysis.[66] 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.[67] 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 (especially subclinical) and low T3 levels.[68] Thyroxine-binding globulin (TBG), T4, and T3 are lost in the PD effluent. Despite continuous and substantial protein loss, TBG levels are normal. The T4 and T3 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 T3 and T4 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 T4 levels lower than the pre-transplant level, before it gradually rises back to normal.[69] In general, post-transplant thyroid volume and free T3 levels correlate well with graft function.[70] Pre-transplant low T3 levels are associated with future risk of graft loss.[71] But therapy with T3 supplementation does not improve graft survival, negating the possibility of a causal association.[72] Thus, there is no need to supplement thyroid hormones for the low T3 levels noted in the first few months of renal transplantation. Thyroid carcinoma is the fifth most common malignancy among kidney transplant patients.[73]

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,[74,75] followed by IgA nephropathy,[76] membranoproliferative glomerulonephritis,[77] and minimal change disease.[78] There are several mechanisms for these associations. The presence of circulating immune complexes among patients with thyroid disease,[79] the association of Hashimoto's thyroiditis and membranous nephropathy with immune complex deposition in the glomerular as well as thyroid epithelial basement membrane,[80] and the common occurrence of thyroid and renal disease in association with other autoimmune diseases such as type 1 diabetes mellitus[81] suggest a common autoimmune 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.[82] 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.[83] Primary hypothyroidism has also been described in congenital nephrotic syndrome, with urinary loss of thyroid hormones resulting in increased TSH level *in utero*.[84]

In addition to the glomerulonephritides mentioned above, isolated cases of hyperthyroidism have been associated with tubulointerstitial nephritis and uveitis (TINU) syndrome.[85] The disease responds well to steroid therapy.

Patients with acute kidney injury may develop an NTI (euthyroid sick syndrome), but without elevation of reverse T3 levels.[86] Hypothyroidism can result in rhabdomyolysis related acute kidney injury.[87]

Thyroid and Renal Malignancy

There is an increased predisposition of patients with thyroid cancer to develop renal cell carcinoma (RCC)[88] due to genetic predisposition or treatment of disease. In addition, thyroid malignancy could metastasize to the kidney[89] and RCC is one of the common tumors metastasizing to the thyroid.[90] While clear cell carcinoma of thyroid, morphologically resembling the RCC, is described, some RCC may morphologically resemble thyroid follicular carcinoma.[91] Thyroid malignancies expressing EPO receptors have favorable prognosis,[92] while

Table 2: Drugs in thyroid and kidney diseases

Drug	Thyroid	Kidney
Thionamide	Hypothyroidism	Glomerulonephritis, vasculitis, lupus nephritis
Alemtuzumab	Autoimmune thyroiditis	Used as induction agent in renal transplantation
Interferon-α	Transient hyperthyroidism	Used for treatment of hepatitis B or C pre-transplant Used in therapy of renal cell carcinoma (RCC) Can accelerate rejection in renal transplant Can precipitate glomerulonephritis/vasculitis
Lenalidomide	Subacute thyroiditis with hyperthyroidism	Used in therapy of RCC
Sunitnib	Hypothyroidism	Used in therapy of RCC
Lithium	Hypothyroidism	Nephrogenic diabetes insipidus Chronic kidney disease (CKD)
^{131}I treatment	Used in therapy of Grave's disease and thyroid carcinoma	Needs dose reduction in CKD and in patients on peritoneal dialysis

RCC expressing aberrant thyroid hormone receptors may contribute to carcinogenesis.[93]

Drugs in Thyroid and Renal Disease

Drugs used in thyroid or kidney disease may have adverse effects on the other organ's functions. Thionamides such as methimazole, carbimazole, propylthiouracil cause hypothyroidism as well as renal dysfunction by immune mechanisms resulting in various glomerular disease such as vasculitis,[94] lupus nephritis,[95] or necrotizing glomerulonephritis with pulmonary hemorrhage.[96]

Alemtuzumab, used in renal transplantation, has been reported to result in autoimmune thyroid disease.[97] Interferon-α, used again in renal cell carcinoma as well as for treatment of hepatitis B and C virus infection pre-transplant causes hyperthyroidism.[98] Lenalidomide, used in renal cell carcinoma for its antitumor and antiangiogenic properties, results in a subacute thyroiditis and transient thyrotoxicosis.[99] Sunitinib, a new therapeutic agent against RCC, results in hypothyroidism, which some authors believe to be associated with better prognosis.[100]

Lithium use causes hypothyroidism as well as nephrogenic diabetes insipidus and CKD. Amiodarone is associated with both hypothyroidism and hyperthyroidism as well as acute renal damage.[101] Rifampicin causes both a tubulointerstitial nephritis as well as hyperthyroidism.[102]

An important consideration is the therapy of hyperthyroid patients with CKD. In general, CKD patients require lower doses of ^{131}I for treatment of Grave's disease. Hyperthyroid patients on HD, due to ^{131}I clearance by dialysis, require the usual therapeutic dose of ^{131}I for treatment.[103] Patients on PD require a fivefold reduction in the ^{131}I dose for treatment of thyroid carcinoma, to avoid excessive radiation.[104] The interactions of various drugs in thyroid and kidney disease are given in Table 2.

Conclusion

There are various mechanisms of interaction between kidney and thyroid functions in the disease states of each other organ. 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 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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