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REVIEW

Thyroid dysfunction and kidney disease

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Abstract

Thyroid hormones (TH) are essential for an adequate growth and development of the kidney. Conversely, the kidney is not only an organ for metabolism and elimination of TH, but also a target organ of some of the iodothyronines' actions. Thyroid dysfunction causes remarkable changes in glomerular and tubular functions and electrolyte and water homeostasis. Hypothyroidism is accompanied by a decrease in glomerular filtration, hyponatremia, and an alteration of the ability for water excretion. Excessive levels of TH generate an increase in glomerular filtration rate and renal plasma flow. Renal disease, in turn, leads to significant changes in thyroid function. The association of different types of glomerulopathies with both hyper- and hypofunction of the thyroid has been reported. Less frequently, tubulointerstitial disease has been associated with functional thyroid disorders. Nephrotic syndrome is accompanied by changes in the concentrations of TH due primarily to loss of protein in the urine. Acute kidney injury and chronic kidney disease are accompanied by notable effects on the hypothalamus–pituitary–thyroid axis. The secretion of pituitary thyrotropin (TSH) is impaired in uremia. Contrary to other non-thyroidal chronic disease, in uraemic patients it is not unusual to observe the sick euthyroid syndrome with low serum triodothyronine (T_3) without elevation of reverse T_3 (rT_3). Some authors have reported associations between thyroid cancer and kidney tumors and each of these organs can develop metastases into the other. Finally, data from recent research suggest that TH, especially T_3, can be considered as a marker for survival in patients with kidney disease.

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Introduction

The interactions between kidney and thyroid functions are known for years (1–4). Thyroid hormones (TH) are necessary for growth and development of the kidney and for the maintenance of water and electrolyte homeostasis. On the other hand, kidney is involved in the metabolism and elimination of TH. From a clinical practice viewpoint, it should be mentioned that both hypothyroidism and hyperthyroidism are accompanied by remarkable alterations in the metabolism of water and electrolyte, as well as in cardiovascular function. All these effects generate changes in water and electrolyte kidney management (5, 6). Moreover, the decline of kidney function is accompanied by changes in the synthesis, secretion, metabolism, and elimination of TH. Thyroid dysfunction acquires special characteristics in those patients with advanced kidney disease (7). 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.

The present article reviews the most important topics of the different derangements in kidney function that occur in patients with thyroid disease, as well as changes in thyroid physiology that develops in patients with kidney disease and with varying types and degrees of kidney failure.

Effects of TH on renal physiology

TH play an important role in growth, development, and physiology of the kidney (8–11; Fig. 1). It is known that hypothyroidism reduces and hyperthyroidism increases the kidney-to-body weight ratio by a not fully understood mechanism (12). 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 (13).

Thyroid function also influences water and electrolyte balance on different compartments of the body (6, 14). The kidney also plays a role on the regulation of metabolism and elimination of TH and is an important target organ for TH actions (2, 15). The decrease in the activity of TH is accompanied by an inability to excrete an oral water overload (16). This effect is not due to an incomplete suppression of vasopressin production, or a decrease in the reabsorptive ability in the dilutor segment of the kidney tubule, but rather to a reduction in the glomerular filtration rate (GFR) (17).

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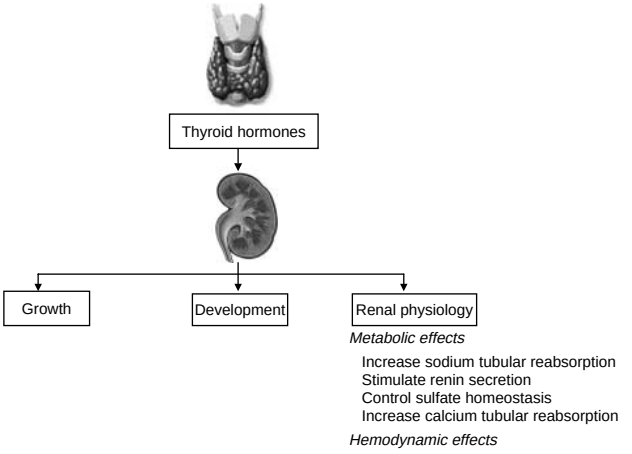

Figure 1 Effects of thyroid hormones on the kidney.

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 (10, 18–23). 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) (18). 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 (24).

TH stimulate renin release by the juxtaglomerular cells through a mechanism independent of the ouabain-sensitive sodium pump and protein synthesis (23) and influence kidney angiotensinase activity (26). 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 (27). Finally, different studies in animals have shown that TH act on the regulation of kidney dopaminergic system (28).

Effects of thyroid dysfunction on the kidney

Thyroid dysfunction causes significant changes in kidney function (Table 1). Both hypothyroidism and hyperthyroidism affect renal blood flow, GFR, tubular function, electrolytes homeostasis, electrolyte pump functions, and kidney structure (2, 15, 29–31).

Hypothyroidism

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. 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 (32).

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 rhEPO action?
Hyponatremia	

rhEPO, recombinant human erythropoietin.

Primary hypothyroidism is associated with a reversible elevation of serum creatinine in both adults (33–35) and children (36, 37). This increase is observed in more than half (~55%) of adults with hypothyroidism (32). Moreover, some authors have reported an elevation of serum creatinine associated with subclinical hypothyroidism (38).

Primary hypothyroidism is associated with a reduction of GFR and RPF that are normalized following levothyroxine administration (14, 15, 29, 32, 33, 37, 39). Similarly, normalization of circulating TH concentrations with replacement therapy in hypothyroid patients with chronic kidney disease (CKD) can significantly improve GFR (40). However, it has recently been reported that kidney function recovers slowly in hypothyroid children, and sometimes partially, after the introduction of replacement with levothyroxine (41). The long-term clinical implications of these findings are unknown.

Hypothyroidism-associated kidney dysfunction seems to be more related with the decline in thyroid hormone levels rather than with thyroid autoimmunity (42). 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 (12, 39, 41).

Hyponatremia is the commonest electrolyte derangement in hypothyroid patients. Hyponatremia appears in 45% of hypothyroid patients who have elevated serum creatinine, but in less than a quarter (21%) of those with normal creatinine levels. It is mainly due to a reduction in GFR causing diminished water delivery to the distal tubular segments. This becomes evident after water load, although ADH may be appropriately

suppressed. Other possible mechanism of hypothyroidism induced hyponatremia is an inappropriate ADH secretion syndrome (SIADH)-like disorder (32, 43).

Thyrotoxicosis

Thyrotoxicosis is characterized by an increase in RPF and GFR resulting in a reduction of serum creatinine levels (12, 44). These changes are normalized after the control of thyroid function with appropriate treatment (14, 15). Hyperthyroidism may be linked to a decrease in total body water and exchangeable K. By contrast, the amount of exchangeable Na tends to increase. 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 (38). However, changes in water and electrolyte metabolism have not been reported by other authors (45).

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 (46).

Kidney disease associated to thyroid dysfunction

The different types of kidney diseases can be associated with various disorders of thyroid function (3, 7).

Glomerular disease

Thyroid disease may be linked to different forms of glomerulonephritis (47–55). Both hypothyroidism (56) and hyperthyroidism (57, 58) can coincide with different forms of glomerular disease. The more frequent form is membranous glomerulopathy associated with nephrotic syndrome (NS) (50, 52, 55–57, 59). Thyroid dysfunction has been reported to be associated with IgA glomerulonephritis (49, 51, 60), mesangiocapillary or membranoproliferative glomerulonephritis (47, 48, 61), and minimal change glomerulonephritis (58, 59, 62, 63).

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 (55–57, 61, 64, 65). The presence of immunocomplexes is common in patients with thyroid disease (66, 67). 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 (67). 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 (55). 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 (61, 63), and iii) the presence of deposits of immunoglobulins and thyroglobulin in the glomeruli of some patients (53, 54, 66). 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.

Tubular disease

Although less frequently than glomerular disease, tubular or tubulointerstitial damage has also been reported to be associated with thyroid dysfunction (68–72). 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 (68–71). 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 (68, 69). Tubulointerstitial nephritis and hyperthyroidism has been reported to be associated in patients under treatment with rifampicin (73).

Nephrotic syndrome

NS is associated with changes in serum TH levels (1, 4, 74, 75). Urinary losses of binding proteins, such as thyroxine binding globulin (TBG), transthyretin or prealbumin, 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 (1). However, patients often remain euthyroid, because free T_4 and T_3 levels are usually normal (1). 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 (1, 74).

Primary hypothyroidism linked to congenital NS (CNS) has been reported (76–81). TH urinary loss associated with the intrauterine massive proteinuria stimulates the hypothalamus–pituitary–thyroid axis increasing serum thyrotropin (TSH) concentrations (76). 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 extrarrenal purification treatment reverses completely the CNS associated hypothyroidism and permits the withdrawal of hormonal treatment with levothyroxine (76). Some authors recommend treatment with levothyroxine supplementation in children with CNS as it facilitates their normal development (81).

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 (7, 82).

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 (83). Furthermore, the development of AKI has been associated with rhabdomyolysis in patients with primary (84, 85) or secondary (86) hypothyroidism treated or not with statins (87).

Chronic kidney disease

CKD affects both hypothalamus–pituitary–thyroid axis and TH peripheral metabolism (86–89) (Fig. 2). Uremia influences the function and size of the thyroid (7, 88, 92–96). Uraemic patients have an increased thyroid volume compared with subjects with normal renal function and a higher prevalence of goiter, mainly in women (7, 93, 96). Also, thyroid nodules and thyroid carcinoma are more common in uraemic patients than in the general population (97).

Serum TSH concentrations are usually normal or elevated in CKD, but its response to its releasing hormone (TRH) is generally low (88, 89, 94, 98, 99). These findings suggest the presence of intrathyroidal and pituitary disturbances associated with uremia (98). Also, both TSH circadian rhythm and TSH glycosylation are altered in CKD. The latter may compromise TSH bioactivity.

Free and total T_3 and T_4 concentrations are usually normal or low in patients with CKD (7, 88, 89, 91, 93, 94, 100). The reduction in T_3 levels (low T_3 syndrome) is the most frequently observed thyroid alteration in these patients (7, 88–90, 92, 99, 101). 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 (102). 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 (103).

In CKD patients, the ESS is characterized by the absence of total rT_3 rising, a typical feature in other patients with non-thyroidal disease (91, 104). Despite the fact that the total rT_3 clearance in CKD patients is diminished, there is a redistribution of rT_3 from the

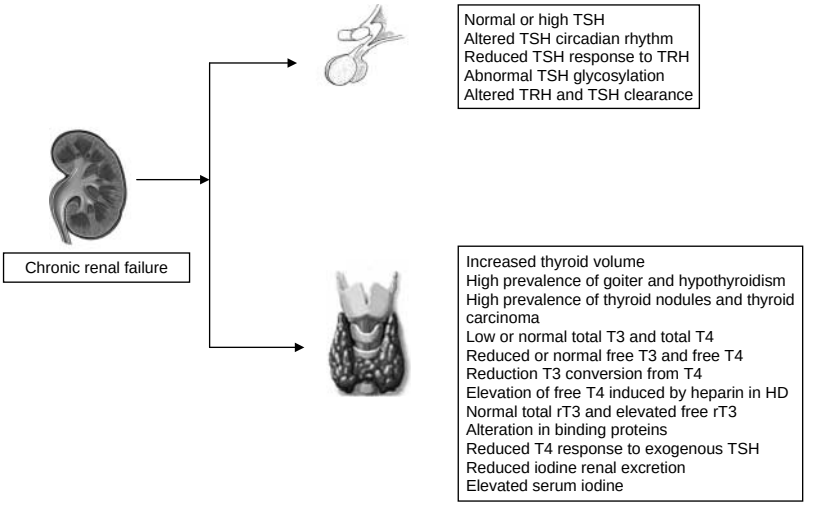

Figure 2 Effects of chronic renal failure on hypothalamus–pituitary–thyroid axis.

vascular to the extravascular space and an increase in rT_3 cellular uptake. However, free rT_3 concentrations are high due to a reduction in its renal clearance (88, 91).

CKD is associated with a higher prevalence of primary hypothyroidism, both overt and subclinical, but not with hyperthyroidism (7, 88, 96, 101). In fact, the prevalence of primary hypothyroidism, mainly in the subclinical form, increases as GFR decreases (101). A recent study has shown a prevalence of subclinical hypothyroidism of 7% in patients with estimated GFR $\geq$90 ml/min per 1.73 m^2 that increased to 17.9% in subjects with GFR $<$60 ml/min per 1.73 m^2 (105). The prevalence of hypothyroidism is higher in women and is associated with an increased frequency of high titers of anti-thyroid antibodies (88).

A greater prevalence of non-autoimmune primary hypothyroidism has been reported in patients with advanced diabetic nephropathy under conservative treatment in comparison with non-diabetic patients with nephropathy. It is possible that these patients had impaired renal handling of iodine resulting in an elevation of serum iodine levels with a prolongation of the Wolff–Chaikoff effect (106).

The prevalence of hyperthyroidism in CKD is similar to that found in general population ($\sim$1%), in areas with inadequate intake of iodine (94). On the other hand, uraemic patients undergoing dialysis with hyperthyroidism due to either Graves' disease or toxic multinodular goiter, can be adequately treated with therapeutic doses of ^{131}I (107, 108). Moreover, hyperthyroidism has been considered as one of the many causes of anemia resistant to recombinant human erythropoietin (rh-EPO) in CKD patients on HD with an adequate response to antithyroid treatment (109).

The kidney contributes to the iodine clearance primarily through glomerular filtration. Serum iodine concentrations are high in CKD but are not correlated with the degree of kidney failure (94). This iodine excess has been linked to increased prevalence of goiter and hypothyroidism reported in CKD (88, 110). A high exposure to iodine facilitates the development of hypothyroidism in CKD patients (111). Some authors have reported that a restriction of dietary iodine in uraemic patients on HD can correct the hypothyroidism avoiding the need for hormone replacement with levothyroxine (112).

Drugs in thyroid and renal diseases

Different drugs used in thyroid diseases may have adverse effects on the kidney, and vice versa, agents used in the treatment of renal disease may develop undesirable effects on the thyroid (Tables 2 and 3). Hypothyroidism induced by thionamides (methimazole, carbimazole, and propylthiouracil) can cause kidney failure. Thionamides can affect kidney function by different immunological mechanisms leading to the development of different types of glomerulonephritis (113–115).

Lithium exerts adverse effects both on the thyroid and kidney, favoring the development of hypothyroidism and nephrogenic diabetes insipidus (DI). Lithium inhibits synthesis and release of TH. Nephrogenic DI induced by lithium may be due to different mechanisms. It may be related to a reduction in levels of aquaporin 2 or to lithium-induced hypercalcemia (116, 117).

The development of autoimmune thyroid disease following the use of alemtuzumab has been reported in transplant patients (118). Treatment with lenalidomide, a new drug with immunomodulatory, antiangiogenic, and antitumor properties, has been associated with transient thyrotoxicosis in patients with metastatic renal-cell carcinoma. The pathogenic mechanism could be that of a subacute thyroiditis (119). Similarly, hyperthyroidism induced by interferon-α has been reported in patients with renal cell carcinoma (120). The use of sunitinib in the treatment of patients with metastatic renal-cell carcinoma can lead to thyroid dysfunction, mainly hypothyroidism (121, 122). Periodic monitoring of thyroid function has been recommended in these patients (121). Since some authors believe that a state of thyroid hypofunction may be associated with a better prognosis in certain tumors, levothyroxine should be prescribed with caution in patients with mild TSH elevation (123).

Thyrotoxicosis induced by sunitinib has been reported in patients with renal cell carcinoma. Some patients may develop hypothyroidism after a transient thyrotoxicosis by sunitinib-induced destructive thyroiditis. The onset of thyrotoxicosis and its severity is unpredictable (124).

Lastly, some drugs can induce adverse effects on the kidney and thyroid. Amiodarone, an iodine-rich antiarrhythmic agent, can cause both hypothyroidism and hyperthyroidism (125, 126), as well as acute renal damage

Table 2 Drugs that can cause thyroid dysfunction and/or renal disease.

Drug	Indication	Thyroid dysfunction	Renal disease
Antithyroid drugs	Hyperthyroidism	Hypothyroidism	Glomerulonephritis
Lithium	Bipolar disorder	Hypothyroidism	Nephrogenic diabetes insipidus
Amiodarone	Arrhythmias	Hypo/hyperthyroidism	Acute kidney injury
Rifampicin	Tuberculosis	Hyperthyroidism	Tubulointerstitial nephritis

Table 3 Drugs used in kidney disease that can affect thyroid function.

Drug	Indication	Thyroid pathology
Alemtuzumab	Renal transplant	Autoimmune thyroiditis
Lenalidomide	Metastasic renal carcinoma	Hyperthyroidism
Sunitinib	Metastasic renal carcinoma	Hypo/hyperthyroidism

(127). As mentioned before, rifampicin can cause tubulointerstitial nephritis and hyperthyroidism (73).

Effects of dialysis on thyroid function

Hemodialysis

Most HD patients are euthyroid. Hypothyroidism is not infrequent in these patients. However, a diagnosis of hypothyroidism in HD patients should not be made solely on the basis of reduced T_4 and T_3 levels but requires documentation of substantial TSH elevation (TSH $>$ 5 mU/l but $<$20 mU/l may occur in 20% of uraemic patients and are more indicative of non-thyroidal illness than hypothyroidism). HD is associated with alterations in the concentration of circulating TH, usually to a reduction in serum total and free T_3 concentrations. This reduction is associated with systemic acidosis, time on dialysis, and some markers of endothelial damage and inflammation (128). Low TH may be a protective adaptation for nitrogen conservation and therefore inappropriate TH supplementation can result in excessive protein nitrogen wasting in these patients. HD influences the cellular transport of TH. This effect could act as a compensatory mechanism to neutralize the thyroid dysfunction in order to maintain euthyroid status (129).

Treatment with ablative dose of ^{131}I has been successfully used in the treatment of differentiated thyroid carcinoma in patients on HD (108, 130–136). HD removes more ^{131}I from blood than from thyroid and helps to reduce radiation (132).

Peritoneal dialysis

The most common thyroid dysfunction in peritoneal dialysis (PD) patients is primary hypothyroidism, especially subclinical hypothyroidism (27.5%) (137) This entity might be implicated in cardiac dysfunction in PD patients due to the fact that these patients show lower left ventricular ejection fractions and fractional shortening at endocardial levels compared with those with normal TSH levels (137). Other common alteration in thyroid function tests is low T_3 syndrome (16%) (138). The high protein loss induced by this type of dialysis could be related to an increased incidence of thyroid dysfunction (139). One of the important issues in PD patients is the continuous loss (due to the continuous nature of the method) of substantial amounts of proteins in the peritoneal cavity. Nevertheless, TBG concentrations remain within normal limits in these patients. When hypothyroidism develops, left ventricular function can be compromised but this is not specific to PD patients.

Because ^{131}I is eliminated primarily by the kidney some authors have recommended a reduction of $\sim$ fivefold in the dose of ^{131}I used in the treatment of differentiated thyroid carcinoma in PD patients to avoid excessive radiation, primarily at bone marrow level (140, 141).

Thyroid function and renal transplantation

Kidney transplantation is associated with abnormalities in thyroid function, mainly a reduction in T_3 concentrations (14–145). An independent relationship between T_3 with different markers of endothelial dysfunction has been reported (143). Both thyroid volume and serum concentration of free T_3 are correlated with the graft function (146–149). A positive correlation between serum creatinine and thyroid volume has been found. Patients with diminished values of T_3 before transplantation are at increased risk of graft failure, thus suggesting that T_3 quantification might be a potential marker for this risk (144, 146, 147, 150). However, treatment with T_3 does not appear to prolong the half-life and function of the graft (151).

Cancer, thyroid and kidney

Patients who have survived to thyroid cancer have an increased risk of suffering a second malignancy, including renal cell carcinoma (152–154). A higher prevalence of genitourinary and kidney tumors has been reported in women with differentiated thyroid carcinoma (154). Coincidental thyroid and renal carcinomas have been reported in an isolated patient (155). This association could be related to the specific treatment of the disease or to a genetic predisposition. Finally, treatment with radiation therapy for a Wilms tumor of the kidney in childhood can be considered as a potential risk factor for developing a differentiated thyroid carcinoma (156).

Owing to the high vascularization of both organs it is not uncommon to observe a renal metastatic spread of a primary thyroid tumor and vice versa. Renal metastases have been reported in patients with papillary (157–163), follicular (164–169), and anaplastic (170) thyroid carcinomas. Kidney metastases from a thyroid carcinoma can appear between 7 and 30 years since diagnosis (168, 169, 171).

Kidney tumors may develop metastases at thyroid level, being between the first and fourth leading cause of thyroid metastases (142, 172–185). The presence of renal cell carcinoma metastases in the thyroid usually indicates a poor prognosis (186, 187), with a mean survival of about 5 years in 64% of cases. However, this type of metastases has also appeared between 5 and 19 years after nephrectomy (188–190).

Approximately, 65% of papillary thyroid carcinomas in children and adolescents express receptors for EPO. Tumors with expression of these receptors show more favorable prognostic indicators than those without them (191). Multiple endocrine neoplasia type 2A (thyroid medullary carcinoma, pheochromocytoma and primary hyperparathyroidism) has been also associated with renal dysplasia (192).

Furthermore, renal cell carcinomas that resemble the morphology of thyroid follicular carcinoma have been reported (193, 194). This histological type has not been recognized as a known form of renal cell carcinoma so far. It would be desirable to keep in mind this histological form to avoid inappropriate or unnecessary treatments (193). On the other hand, clear cell thyroid carcinomas have also been reported (195).

Some authors have observed not only changes in the role of nuclear receptors of TH in the renal cell carcinoma cells, but also aberrant patterns of expression of these receptors. It has been suggested that these abnormalities could contribute to the carcinogenesis of this type of tumor (196).

Finally, transplant patients show higher risk of oncogenesis than that found in the general population (197). The incidence of thyroid carcinoma in this group of patients has been found to be increased (198). In some populations, thyroid carcinoma is the fifth leading cause of malignancy in these patients (199).

Thyroid function, morbidity, and mortality in kidney disease

There is a relationship between plasma levels of T_3 and various markers of inflammation, nutrition, and endothelial activation in patients with CKD (200). These patients show an association between low serum values of T_3 with inflammation markers (elevated levels of high sensitivity C-reactive protein, hs-CRP; interleukin 6, IL-6; and vascular adhesion molecule-1, VCAM-1) and nutrition (decrease of albumin and IGF-1), and cardiac function. The lower the concentration of T_3 the greater the degree of inflammation, and poorer the nutritional status and cardiac function. Therefore, low T_3 is associated with a survival disadvantage. The relationship between survival and T_4 is less defined.

A reduction in total T_3, but not in free T_3 concentrations was associated with an increased all-cause and cardiovascular mortality in euthyroid CKD patients (200). Total and free T_3 behave as survival markers in patients with CKD both in HD (201) and in PD (202). For these reasons, some authors have recommended measuring T_3 levels to assess the relationship between thyroid dysfunction and risk of mortality in this population. Finally, it has been recently reported that low levels of T_3 before renal transplantation are associated with decreased survival of the graft (150).

Several factors, including malnutrition and intercurrent processes, may be involved in the reduction of serum T_3 in uraemic patients. Fasting and disease alter iodothyronine deiodination, thus reducing peripheral production of T_3. The presence of chronic protein malnutrition is associated with a reduction of binding protein synthesis and could reduce plasma total T_3 concentration. TNFα and interleukin-1 inhibit the expression of type 1 5′-deiodinase, the enzyme responsible for T_4 to T_3 conversion in peripheral tissues. This would explain how chronic inflammation and vascular damage associated to CKD interfere with the normal process of T_3 synthesis from T_4 (142, 200, 201–203).

Conclusions

In summary, kidney and thyroid function and dysfunction are interrelated through several mechanisms.

From a clinical practical perspective, in patients with kidney disease, it is generally sufficient to use thyroid function tests commonly used in the clinic. However, to avoid mistakes in diagnosis, it is important to know the effects of hypothyroidism and hyperthyroidism on renal function, as well as the changes in thyroid function tests induced by acute and chronic kidney diseases. Drugs used in the treatment of thyroid and kidney diseases may induce changes in renal and thyroid physiology respectively. Treatment of CKD by HD, PD or renal transplantation is also accompanied by specific changes in thyroid physiology. In patients with differentiated thyroid carcinoma, some modifications in the usual therapies may be necessary, especially in the dose of I^{131}, in the presence of a decline in renal function. On the other hand, recent investigations have shown interesting relationships in neoplastic diseases affecting the thyroid and the kidney. A relationship between T_3 levels and mortality has been proven in uraemic patients; however, the relationship between TSH and survival, well established in other population groups, has not been reported in patients with different degrees of kidney insufficiency. 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.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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