The Renal Manifestations of Thyroid Disease

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ABSTRACT

Thyroid hormones influence renal development, kidney structure, renal hemodynamics, GFR, the function of many transport systems along the nephron, and sodium and water homeostasis. These effects of thyroid hormone are in part due to direct renal actions and in part are mediated by cardiovascular and systemic hemodynamic effects that influence kidney function. As a consequence, both hypothyroidism and hyperthyroidism associate with clinically important alterations in kidney function and have relevance to its assessment. Disorders of thyroid function have also been linked to development of immune-mediated glomerular injury, and alterations in thyroid hormones and thyroid hormone testing occur in patients with kidney disease.

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Thyroid hormone affects nearly every organ system in the body. It is produced and secreted by the thyroid gland under the control of the anterior pituitary hormone thyroid stimulating hormone (TSH), which is, in turn, regulated by hypothalamic thyrotropin-releasing hormone. Thyroxine (T4) is produced only by the thyroid gland, whereas triiodothyronine (T3), the more biologically active form of thyroid hormone, is produced primarily through local deiodination of T4 by the enzyme T4-5′-deiodinase in other tissues, including the kidney. The kidney contains the D1 isoform of this enzyme, which becomes less active in uremia.[1] Thyroid hormone exerts its effect primarily through binding to thyroid hormone nuclear receptors, which then affect gene transcription by binding to thyroid hormone response elements of target genes. Thyroid hormones can also exert nongenomic effects by binding to elements on the plasma membrane and cytoplasm.[2,3]

IMPACT OF THYROID HORMONE ON RENAL GROWTH AND DEVELOPMENT

In experimental animals, the availability of thyroid hormone affects kidney size, weight, and structure both during development and in adults. Histologic studies document the effects of thyroid hormone on cortical and outer medullary tubular segments, particularly involving the proximal tubule, distal convoluted tubule, and medullary thick ascending limb.[4–6] In neonatal rats, hypothyroidism decreases kidney size and weight, tubule length and diameter, and, to a lesser extent, glomerular volume.[7–9] These changes invariably reverse with thyroid hormone replacement. Hypothyroidism also blunts compensatory hypertrophy after unilateral nephrectomy in remnant kidney models.[10,11] Conversely, kidney to body weight ratios in hyperthyroid animals increase by as much as 30%.[12,13]

Children with congenital hypothyroidism have reduced renal mass and a higher prevalence of renal and urologic abnormalities, including dysplastic kidney, renal agenesis, ectopic kidney, hydronephrosis, posterior urethral valves, and hypospadias.[14] Mutations in the gene encoding *Pax8*, a transcription factor important for normal development and function, may, in some patients, be the link between congenital hypothyroidism and renal dysmorphogenesis.[15]

Although the exact mechanisms of the changes in kidney size are unknown, there is evidence that direct activation of the renin–angiotensin–aldosterone system by thyroid hormone can be independent of effects on hemodynamics.[12] Kobori *et al.*[16] have demonstrated that renal hypertrophy seen in hyperthyroid rats is blocked with losartan but not with nicardipine. This group has also demonstrated that the promoter activity of the renin gene in Calu-6 cells is stimulated by thyroid hormone through a thyroid hormone response element–dependent mechanism, increasing expression of mRNA encoding renin.[16] Whether some renin–angiotensin–aldosterone system

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component serves directly or indirectly as a thyroid hormone–modifiable growth factor is unclear.

Thyroid hormone is also important in the development of tubular function in both the prenatal and postnatal periods. In experimental animals, thyroid hormone affects the maturation, activity, and density of the Na^+-Pi cotransporter, increases Na^+-H^+ exchanger and Na^+-K^+-ATPase activity, and plays a role in the isoform switch from neonatal Na^+-H^+ exchanger 8 to adult Na^+-H^+ exchanger 3.[17–20]

DIRECT EFFECTS OF THYROID HORMONE ON RENAL TUBULAR FUNCTION

Thyroid hormone directly influences the expression and/or activity of a number of ion channels and transporters (Table 1). In some cases, this is due to direct binding of thyroid hormone to the promoter region of a transporter gene.[21] Examples of the effects of these changes can be seen clinically in both hyperthyroid and hypothyroid patients.

Hyperthyroidism is associated with polyuria, which is due to a combination of direct downregulation of aquaporin 1 and 2 along with increased BP, cardiac output, and renal blood flow. Food and water intake are also increased, as is catabolic rate. All of these factors may increase distal delivery of sodium, despite upregulation of the Na^+-K^+-$2Cl^-$ cotransporter, other solutes, and water, resulting in increased urine flow rate.[13]

Table 1. Renal tubular ion transporters affected by thyroid hormone

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

Transporter function is decreased with hypothyroidism and increased with hyperthyroidism or thyroid hormone replacement with the exception of AQP, which has the opposite pattern.[54–60] AQP, aquaporin.

Hyponatremia due to impaired water excretion is a common complication of clinical hypothyroidism. Studies in hypothyroid animals demonstrate reduced capacity to achieve maximal urinary dilution due to nonosmotic arginine vasopressin release, as well as impaired urinary concentrating ability, increased urinary sodium excretion, increased fractional excretion of sodium, and impaired tolerance of sodium restriction.[22] These animals exhibit decreased Na^+-H^+ exchanger and Na^+-Pi cotransporter activity. Micropuncture studies also show reduced sodium reabsorption in both proximal and distal tubule segments, abnormalities that are corrected with thyroid hormone replacement.[22,23] A small study in five hypothyroid men given an acid load demonstrated a decreased ability to acidify the urine.[24]

HEMODYNAMIC CHANGES IN THYROID DISEASE

That thyroid disease exerts dramatic effects on the cardiovascular system has been known for many decades.[25–27] Thyroid hormone directly affects cardiac myocytes by regulating genes important for myocardial contraction and electrochemical signaling, including positively regulating sarcoplasmic reticulum Ca^{2+}-ATPase, α-myosin heavy chain, β1-adrenergic receptors, guanine nucleotide regulatory proteins, Na^+-K^+-ATPase, and voltage-gated potassium channels and negatively regulating β-myosin heavy chain, phospholamban, Na^+-Ca^{2+} exchanger, and adenylyl cyclase types V and VI.

Thyroid hormone also affects vascular smooth muscle tone and reactivity. Most importantly, nitric oxide synthase activity increases in the kidney, heart, aorta, and cava in hyperthyroid rats. Hypothyroid rats showed a more mixed picture, with reduced activity in the aorta and cava but increased activity in the heart and stable activity in the kidney.[28] Hypothyroid animals also exhibit a decreased sensitivity to adrenergic vasoconstrictors and endothelium-dependent vasodilators.[27,28]

As a consequence of these cardiac and vascular effects, hyperthyroidism can increase cardiac output up to threefold by increased heart rate, increased inotropy, and decreased systemic vascular resistance.[26] Not surprisingly, renal blood flow also increases by direct measurement in hyperthyroid rats.[13] Opposite but equally dramatic hemodynamic effects occur in hypothyroid patients and experimental animals.[26] In adult animals, hypothyroidism (generally the result of thyroidectomy) reduces single nephron GFR, renal plasma flow, and glomerular transcapillary hydrostatic pressure.[10,29]

GFR AND THYROID DYSFUNCTION

Many case reports and small case series document increased levels of serum creatinine with hypothyroidism in humans.[30–34] The importance of understanding the impact of thyroid dysfunction on renal function is highlighted by recent studies indicating subclinical and clinical hypothyroidism is common in patients with estimated GFR < 60 ml/min per 1.73 m^2, begging the question of whether hypothyroidism might be contributing to the low GFR in some of these individuals.[35,36]

Serum creatinine levels in excess of 6 mg/dl have been attributed to hypothyroidism, with a few patients even described as having ESRD, although in most reports, creatinine levels have been in the range 1.5–2.5 mg/dl. Elevation of levels of serum creatinine can occur within as little as 2 weeks of significant hypothyroidism. These levels typically normalize rapidly with thyroid hormone replacement after short periods of hypothyroidism,[33] but slower and incomplete recovery has been noted with more prolonged periods of severe hypothyroidism. Similarly, multiple human and animal studies demonstrate a decreased serum creatinine in the setting of hyperthyroidism, which is similarly reversible upon treatment.[34]

Most of these case reports, however, rely on estimations of kidney function using creatinine-based estimating equations, so the extent to which these changes reflect changes in true GFR as opposed to alterations in creatinine metabolism or tubular secretion or to an underlying myopathy has been unclear. Karanikas and colleagues[37] performed ^{51}Cr-EDTA isotopic renal scans in thyroidectomized patients with severe hypothyroidism (mean TSH 70±23 μIU/ml) before and after thyroid hormone replacement. A fall in serum creatinine with thyroid hormone replacement (1.30±0.44 versus 1.04±0.32 mg/dl) was associated with an increase in GFR by ^{51}Cr-EDTA clearance (61±18 versus 75±23 ml/min). In another study of hypothyroid patients, estimated renal plasma flow, measured by ^{131}I-hippuran clearance, increased from 542.8±215.8 to 717.0±140.6 ml/min per 1.73m^2, and GFR, measured with ^{52}Cr-EDTA clearance, increased from 99.6±32.2 to 125.7±41.2 ml/min after thyroid hormone replacement,[38] thus confirming that changes in levels of serum creatinine in patients with thyroid disorders do reflect actual changes in GFR. These changes in GFR are likely due to a number of factors (Figure 1).

Cystatin C is a cysteine proteinase inhibitor that is produced at a constant rate by most nucleated cells, freely filtered at the glomerulus, and then reabsorbed and metabolized by proximal tubular epithelial cells.[39] Somewhat surprisingly, studies in humans and animals show that serum cystatin C levels generally trend in the opposite direction to those of creatinine[40,41]; that is, cystatin C is commonly elevated in hyperthyroid patients and decreased in hypothyroid patients. This pattern has been demonstrated in a wide range of causes and severity of thyroid diseases[42] and is hypothesized to be a direct effect of thyroid hormone on cystatin C production, although the exact mechanism is not known. Cystatin C should not be used for assessment of GFR in patients with thyroid disease.

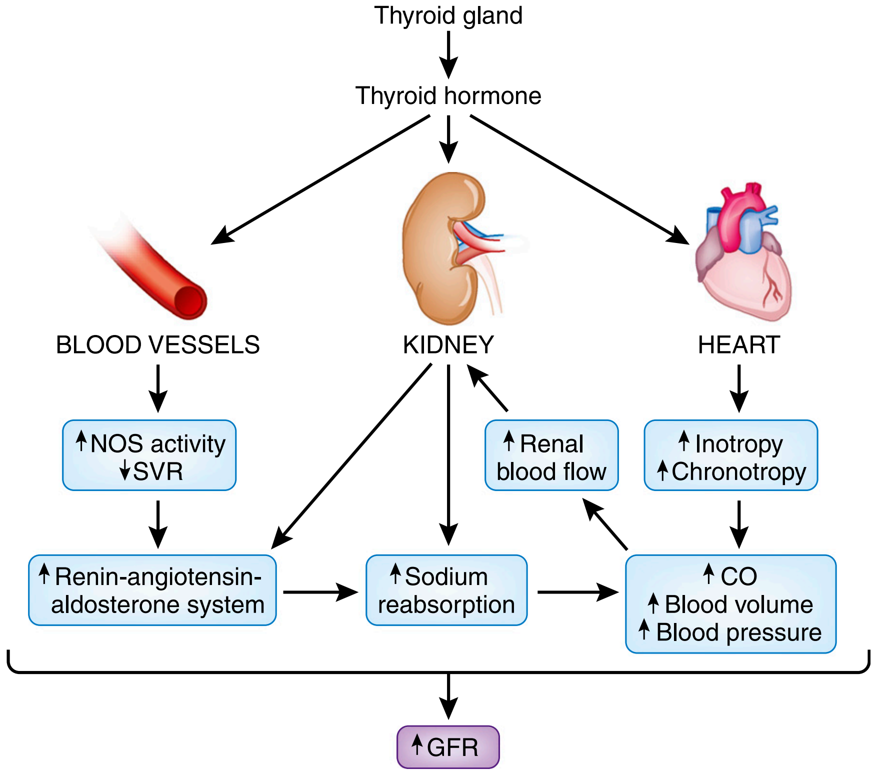

Figure 1. Multiple direct and indirect effects of thyroid hormone on GFR. NOS, nitric oxide synthase; SVR, systemic vascular resistance; CO, cardiac output.

GLOMERULAR DISEASE IN PATIENTS WITH THYROID DISEASE

Isolated cases of reversible proteinuria and biopsy-proven GN associated with hypothyroidism and hyperthyroidism, most commonly in relationship to autoimmune thyroiditis, are reported in animals, as well as children and adults.[30] Where available, renal histopathology has revealed membranous nephropathy, minimal change, membranoproliferative GN, and IgA nephropathy. Whereas a direct pathogenic link between autoimmune thyroid disease and glomerular disease is uncertain, immune-mediated processes affecting both have been proposed, and there are reports of thyroid peroxidase and thyroglobulin deposits in the kidney.[43] Glomerular disease has also been described after therapy for hyperthyroidism: specifically, antineutrophil cytoplasmic antibody-positive crescentic GN after therapy with propylthiouracil[44] and membranous nephropathy after ^{131}I treatment.[45]

THYROID FUNCTION TESTS IN PATIENTS WITH KIDNEY DISEASE

The kidney plays a role in clearance of iodine, TSH, and thyrotropin-releasing hormone. However, most patients with CKD are euthyroid, with normal TSH and free T4 levels. Patients with AKI and some with advanced CKD may have changes in thyroid function tests consistent with the euthyroid sick syndrome; that is, low T4, T3, and TSH concentrations.[30,46,47] Unlike most patients with euthyroid sick syndrome, those with renal failure typically have normal rather than increased reverse T3 levels.[30,46] ESRD patients have decreased levels of free T3.[48] These changes seen in patients with CKD and ESRD are due to alterations in the peripheral 5′-monodeiodination of T4, reduced levels of plasma proteins that bind T4, the presence of inhibitors of T4 binding to plasma proteins, metabolic acidosis, and effects of medications.[48–50] Heparin and furosemide, among other drugs, inhibit T4 binding to plasma proteins and may transiently elevate free T4 levels.[51] Thyroid gland enlargement, thyroid nodules, and thyroid carcinoma are also more common in patients with severe CKD than in the general population.[52]

Patients with nephrotic syndromes have urinary losses of proteins that bind thyroid hormones, including thyroxine binding globulin, transthyretin, and albumin.[30] This can result in reductions in total plasma T4 and less commonly total T3 levels that are roughly proportional to the severity of hypoalbuminemia and degree of proteinuria.[30] Many such patients remain euthyroid, however, as the result of increased secretion of TSH and thyroid hormone synthesis, although clinical hypothyroidism can occur.[53] Patients with nephrotic syndrome who are on exogenous thyroid hormone replacement may need an increase in their levothyroxine dose to maintain a euthyroid state.[30]

Thyroid hormones influence renal development, kidney structure, renal hemodynamics, GFR, the function of many transport systems along the nephron, and sodium and water homeostasis. Effects of hypothyroidism and hyperthyroidism on kidney function are the result of direct renal effects, as well as systemic hemodynamic, metabolic, and cardiovascular effects. Fortunately, most of the renal manifestations of thyroid disorders, which are clinically most significant with hypothyroidism, are reversible with treatment. Patients with hypothyroidism can have clinically important reductions in GFR, so screening for hypothyroidism should be considered in patients with unexplained elevations in serum creatinine. Serum cystatin C levels are not accurate indicators of GFR in such patients, however, and the accuracy of serum creatinine–based estimating equations in patients with hypothyroidism also is uncertain. Patients with thyroid disorders are also at risk for immune-mediated glomerular diseases. Finally, patients with nephrotic syndrome, as well as acute and chronic kidney injury, have alterations in thyroid gland physiology that can impact thyroid function and the testing of thyroid function status.

DISCLOSURES

None.

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