

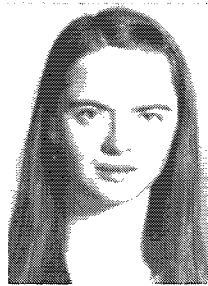
# THYROID TODAY<sup>®</sup>

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## CHANGES IN THYROID HORMONE PHYSIOLOGY IN RENAL DISEASES

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### Potential Role of the Kidney in Peripheral Thyroid Hormone Metabolism

The normal thyroid gland produces primarily thyroxine (T<sub>4</sub>), with the majority of triiodothyronine (T<sub>3</sub>) and reverse T<sub>3</sub> (rT<sub>3</sub>) being derived from enzymatic deiodination of T<sub>4</sub> in the tissues.<sup>1</sup> The presence of 5'- and 5-deiodinase enzymes has been demonstrated in the kidney, as well as in the liver, skeletal muscle, heart, and brain.<sup>2,3</sup> These tissues also are capable of disposing of these thyroid hormones by deiodination, conjugation with sulfate or glucuronic acid, and side-chain metabolism.<sup>4</sup> Although the kidney is capable of participating in all aspects of peripheral thyroid hormone metabolism, its quantitative contribution to the production of T<sub>3</sub> and rT<sub>3</sub> and to thyroid hormone degradation *in vivo* is not established. In addition, intact thyroid hormones are filtered, reabsorbed, and secreted by the kidney and a major route of iodide elimination is by urinary excretion.<sup>4</sup>

### Thyroid Hormone Metabolism in Chronic Renal Failure

Chronic uremia is associated with a number of conditions that may affect thyroid hormone metabolism. These include the state of chronic nonthyroidal illness, malnutrition and negative nitrogen balance,<sup>5</sup> the presence of circulating inhibitors of physiologic functions,<sup>6-8</sup> and a multitude of hormonal alterations.<sup>9</sup> In addition, dialysis and drug therapies may influence thyroid hormone metabolism.

Patients in chronic renal failure (CRF) frequently display abnormalities in serum concentrations of thyroid hormones. The levels of total T<sub>4</sub> (TT<sub>4</sub>) and total T<sub>3</sub> (TT<sub>3</sub>) tend to decrease as renal insufficiency progresses.<sup>10-12</sup> In 30% of 199 patients with end-stage renal failure, prior to dialysis therapy, the serum levels of TT<sub>4</sub> were reported to be decreased below the normal

range<sup>12-21</sup>; serum levels of free T<sub>4</sub> by equilibrium dialysis usually were normal.<sup>11,16,21-23</sup> During chronic hemodialysis therapy, serum TT<sub>4</sub> levels were decreased in 43% of 479 patients.<sup>15,18,24,25</sup> Serum concentrations of TT<sub>3</sub> were reduced in 50% of 177 uremic patients prior to dialysis<sup>12,14,16,20,26</sup> and in 37% of 345 patients receiving chronic hemodialysis therapy.<sup>16-18,20,21,23,25-31</sup> The serum levels of free T<sub>3</sub> also were decreased in these patients.<sup>22-29</sup> In contrast to the elevated total rT<sub>3</sub> (TrT<sub>3</sub>) values observed in patients with nonrenal nonthyroidal illnesses,<sup>22</sup> patients with CRF usually have normal total serum rT<sub>3</sub> concentrations<sup>19,21,22,32</sup> with elevated levels of free rT<sub>3</sub>.<sup>22,32</sup> Since the serum concentrations of thyroxine-binding globulin (TBG) are typically normal in these patients,<sup>11,13,14,16,23,26,33</sup> the decreased serum levels of TT<sub>4</sub> and TT<sub>3</sub>, the normal TrT<sub>3</sub> values, and the increased free fractions of T<sub>4</sub>, T<sub>3</sub>, and rT<sub>3</sub> by equilibrium dialysis<sup>11,22,23,30,32</sup> could be at least partially due to inhibition of hormone binding to TBG. Indeed, uremic serum contains inhibitors of many biological functions<sup>7-9</sup> and it is possible that inhibitors of thyroid hormone binding to carrier proteins may also exist as they do in patients with other nonthyroidal illnesses.<sup>34</sup> The serum thyroid-stimulating hormone (TSH) values are reported to be normal<sup>12,14,16-20,24,26,28,30,33,35</sup> or only minimally elevated,<sup>23,25,31</sup> while the TSH responses to thyrotropin-releasing hormone (TRH) are normal or blunted<sup>14,25,26</sup> in patients with CRF both prior to and during dialysis therapy.

A few serum kinetic studies of thyroid hormones have been carried out in patients with chronic renal failure. These data indicate normal metabolic clearance and disposal rates of T<sub>4</sub> both before and during treatment with maintenance dialysis.<sup>26,32,36</sup> In addition, these patients have a reduced TT<sub>4</sub>/TBG ratio in association with a decreased fractional rate of T<sub>4</sub> exit from serum,<sup>32</sup> a discrepancy also observed in patients with acute nonrenal nonthyroidal illnesses.<sup>37</sup> A reduction of T<sub>4</sub> binding to serum carrier proteins should lead to an increased fractional rate of T<sub>4</sub> exit from serum, as observed in healthy euthyroid subjects with decreased serum TBG concentrations.<sup>37</sup> The mechanisms responsible for these paradoxical observations in patients with nonthyroidal illnesses remain to be defined. Serum kinetic studies of T<sub>3</sub> both before and during chronic hemodialysis therapy indicate that the production rates of T<sub>3</sub> are markedly reduced secondary to impaired peripheral conversion of T<sub>4</sub> to T<sub>3</sub>.<sup>26</sup> This accounts for the low serum total and free T<sub>3</sub> levels reported in these patients.

Disturbances in thyroid hormone indices similar to those

seen in patients with CRF are also observed in patients without renal disease who are suffering from a wide variety of catabolic states due to acute and chronic nonthyroidal illnesses.<sup>38,39</sup> These patients also may have decreased serum TT4 and normal free T4 levels.<sup>38,39</sup> The magnitude of the decrease in TT4 is related to the severity of the illness and to the prognosis.<sup>40</sup> Serum levels of total and free T3 are also markedly reduced in these patients.<sup>22,37,38</sup> In addition, patients with nonrenal nonthyroidal illnesses have alterations in their peripheral metabolism of T4 and T3<sup>37</sup> that resemble those seen in CRF. These observations suggest that the abnormalities in T4 and T3 metabolism in uremia may be due, at least in part, to the state of nonthyroidal illness rather than to the uremia, per se.

In contrast, uremia may result in unique alterations in the metabolism of rT3. The serum levels of TrT3 are elevated in the majority of patients with acute and chronic nonthyroidal diseases.<sup>38,39</sup> This is due to reduced serum clearance of rT3 and not to increased rT3 production, since the latter is normal.<sup>37,41</sup> In contrast, patients with CRF have normal total<sup>19,21,22</sup> and elevated free<sup>22,32</sup> rT3 levels. The reasons for this difference are not obvious, and one must assume that in uremia additional factors are operative that affect rT3 metabolism. These may include: reduced rT3 production by the decreased renal functioning mass, severe impairment of serum binding, and/or accelerated serum clearance of rT3.

We have evaluated the peripheral distribution and metabolism of rT3 in patients with end-stage CRF and found:

- Normal production rates.
- Mild impairment of binding to serum proteins.
- Markedly increased extravascular binding of rT3.<sup>32</sup>

These data indicate that the normal total serum rT3 levels in patients with CRF are not related to reduced production by the abnormal kidney but are due to a shift of rT3 from serum to tissue which may be, in turn, secondary to augmented tissue binding of the hormone.

Despite the reduced serum levels of total and free T3 in uremic patients, they appear to be euthyroid. This is evidenced by normal serum levels of free T4 and TSH, the absence of an exaggerated TSH response to TRH, normal clinical index score, basal metabolic rate, systolic time interval, and relaxation time of Achilles tendon reflex.<sup>23,24</sup> This does not necessarily mean that the low T3 state has no clinical significance in these patients. It is possible that the decreased serum free T3 levels provide a protective mechanism against the catabolic effects of chronic uremia. A similar role for the low serum T3 levels has been postulated in other nonthyroidal illnesses as well as during fasting.<sup>42</sup> It should be mentioned, however, that studies of the uremic rat indicate the presence of tissue hypothyroidism of the liver that may be specifically related to T3 deficiency<sup>43</sup> in association with a normal T3 content of the pituitary.<sup>44</sup> It is not known whether specific tissue hypothyroidism occurs during the low T3 state in man.

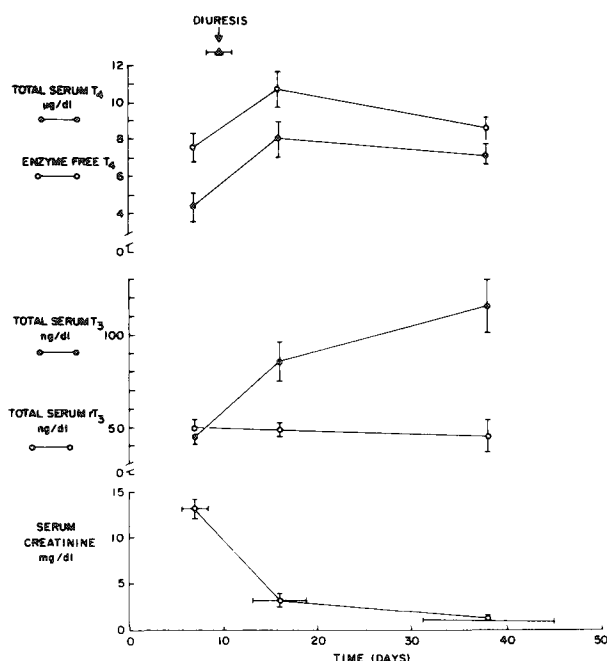
A high incidence of goiter has been reported among CRF patients in Utah,<sup>33</sup> Illinois,<sup>26</sup> South Africa,<sup>25</sup> and Israel,<sup>31</sup> but was infrequently encountered in Maryland,<sup>23</sup> Alberta, Canada,<sup>24</sup> London, England,<sup>30</sup> and Denmark.<sup>12</sup> The geographical variations would suggest that the genesis of goiter in chronically uremic patients is not related to uremia per se but to environmental goitrogenic factors.<sup>4</sup> An autoimmune etiology for the thyroid enlargement appears unlikely since antithyroid antibodies are usually absent in these patients.<sup>16,24,26,33</sup>

#### Thyroid Hormone Metabolism in Acute Renal Failure

Patients with oliguric acute renal failure (ARF), who do not have other major systemic disorders, display abnormalities in

serum thyroid hormone indices<sup>45</sup> similar to those observed in patients with CRF. They may have decreased serum levels of TT4 and TT3, normal free T4 and TrT3, and elevated free rT3 values. These findings are consistent with the presence of decreased serum binding of T4 and rT3 to their serum carrier proteins. Serum TSH concentrations are normal and the TSH responses to TRH are blunted during the oliguric phase compared with the response after recovery of renal function.

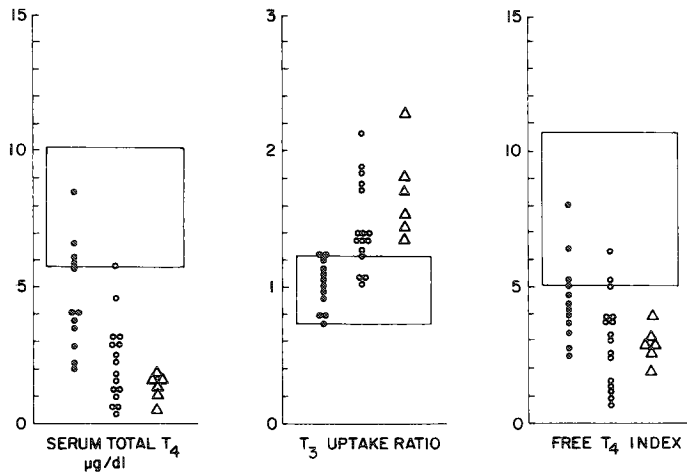
These alterations occurred within a few days after the onset of ARF (Figure 1). The lowest values for TT4 ( $4.4 \pm 0.8 \mu\text{g/dl}$ ) were observed during the oliguric phase,  $6.5 \pm 1.4$  days after the onset of the ARF. There was a significant inverse correlation between the serum TT4 and creatinine levels during the oliguric phase. During recovery, the serum TT4 values returned to normal with the highest values ( $7.9 \pm 1.0 \mu\text{g/dl}$ ) occurring  $6.5 \pm 1.3$  days after the onset of diuresis. The serum TT3 levels were lowest during the oliguric phase and increased towards normal with the onset of diuresis, although the mean value ( $85 \pm 11 \text{ ng/dl}$ ) during diuresis remained significantly lower than normal ( $147 \pm 3 \text{ ng/dl}$ ).



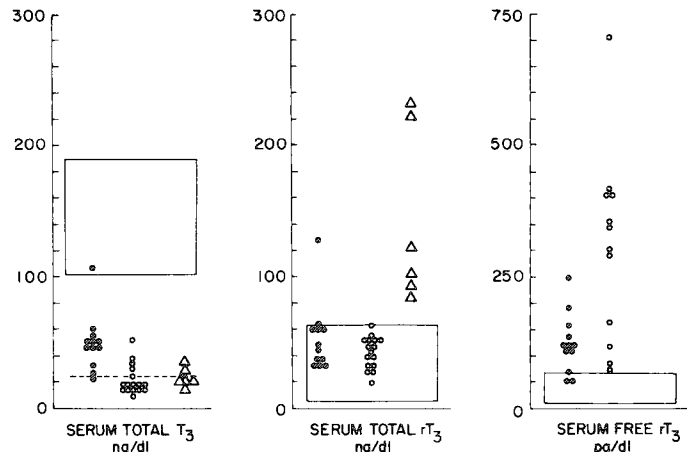
**Figure 1**  
The changes in the serum concentrations of total T4, T3, rT3, free T4 by enzyme immunoassay, and creatinine during the oliguric and diuretic phases of acute renal failure and after recovery of renal function in eight patients without critical illnesses. Values during oliguria represent those associated with the lowest serum total T4 levels; values during the diuretic phase and after recovery of renal function are associated with the highest serum concentrations of total T4. Brackets represent mean  $\pm$  SE. (By permission from Kaptein et al.<sup>45</sup>)

Patients with ARF are acutely ill in addition to having acute renal insufficiency and, on this basis alone, would be expected to develop abnormalities of thyroid hormone indices. We have examined the role of ARF per se, and that of associated acute illnesses in the genesis of the derangements. Patients with ARF, in the presence and absence of acute critical illnesses, were compared with those with acute critical illnesses without renal failure.<sup>45</sup> The values of the thyroid hormone indices in these three groups of patients are shown in Figures 2 and 3. Although patients in each group had decreased serum levels of TT4 and TT3, these indices were significantly lower in the patients with ARF in the presence of critical illnesses and in those with critical illnesses alone than in patients with ARF alone. Despite the low levels of TT3, serum TrT3 levels are normal in pa-

tients with ARF in the presence or absence of an associated acute critical illness as compared with the elevated values of TrT3 in all patients with acute critical illnesses and normal renal function. These observations further indicate that uremia has a predominant influence on the metabolism of rT3.



**Figure 2** Serum total T4, T3 uptake ratio, and free T4 index values in patients with acute renal failure without critical illness (●), acute renal failure with critical illness (○), and critical illness without renal failure (△). Open rectangles represent the normal range of values. (By permission from Kaptein et al.<sup>45</sup>)

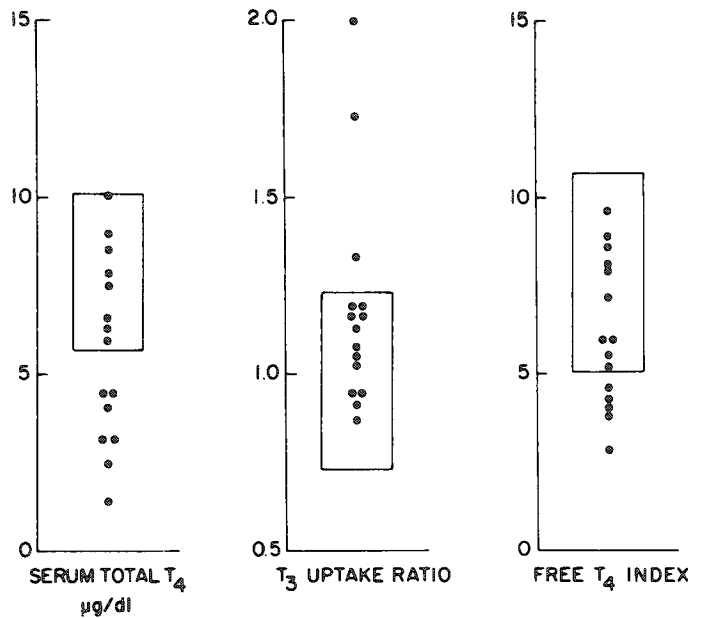


**Figure 3** Serum total T3, total rT3, and free rT3 concentrations in patients with acute renal failure without critical illness (●), acute renal failure with critical illness (○), and critical illness without renal failure (△). Open rectangles represent the normal range of values. The dash line represents the lower assay limit. (By permission from Kaptein et al.<sup>45</sup>)

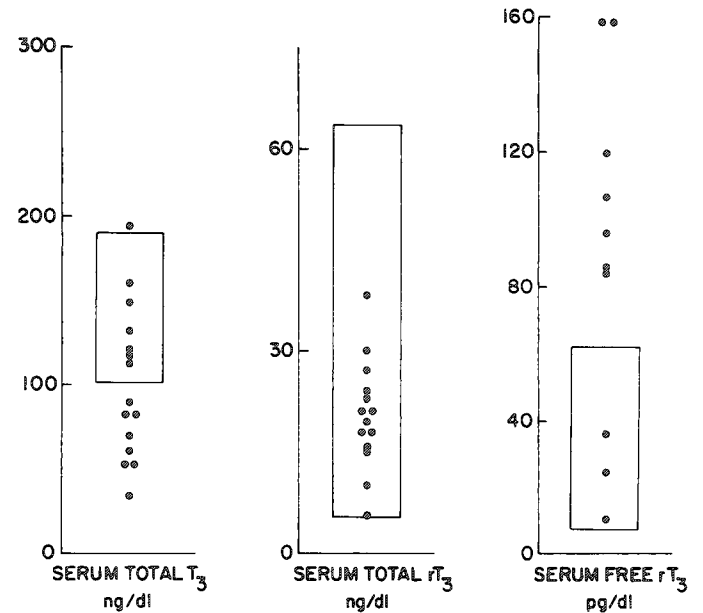
### Thyroid Hormone Metabolism in the Nephrotic Syndrome

A number of alterations of thyroid hormone indices have been reported in patients with the nephrotic syndrome.<sup>46-48</sup> These included decreased serum levels of TT3 and TT4 with normal levels of TBG, TrT3, free T4, and TSH. Many of these changes are similar to those found in other nonthyroidal illnesses and in those with acute and chronic renal failure as described above. Since the majority of the patients with nephrotic syndrome in whom these thyroid hormone indices have been reported were either diabetics<sup>46</sup> or had renal insufficiency,<sup>46,47</sup> it is difficult to ascertain whether the reported changes in thyroid hormone indices are due to the nephrotic syndrome per se or the associated disease states. We have evaluated the role of nephrotic syndrome per se in 15 nephrotic patients with normal glomerular filtration rates, who did not have other associated

diseases that would affect thyroid hormone indices.<sup>48</sup> The serum thyroid hormone indices are shown in Figures 4 and 5. The serum levels of TT4 and TT3 are reduced in approximately one half of the patients while the levels of TrT3 are normal in all. The levels of free T4 by equilibrium dialysis are normal or elevated and free rT3 values are increased in seven of ten patients. The basal levels of TSH as well as the peak TSH response to TRH are normal. These data clearly indicate that the nephrotic syndrome per se is associated with alterations in thyroid hormone indices. The normal serum free T4 values in the presence of normal TBG levels in nephrotic patients with low serum TT4 values is consistent with decreased serum T4 binding to TBG.<sup>46-48</sup> The decrement in the serum levels of TT3



**Figure 4** Serum levels of total T4, T3 uptake ratio, and free T4 index in 15 patients with nephrotic syndrome and normal glomerular filtration rates. Open rectangles represent the normal range of values. (By permission from Feinstein et al.<sup>48</sup>)



**Figure 5** Serum levels of total T3 and total rT3 in 15 patients with nephrotic syndrome and normal glomerular filtration rates, and serum levels of free rT3 in ten of these patients. Open rectangles represent the normal range of values. (By permission from Feinstein et al.<sup>48</sup>)

also could be related to reduced binding to TBG. In addition, decreased T3 production could be responsible for the reduced serum levels, as has been shown in other nonthyroidal illnesses.<sup>26</sup> Gavin et al<sup>26</sup> reported a reduced TT3/TT4 serum ratio in patients with nephrotic syndrome, an observation compatible with impaired T3 production. It should be noted that seven of their ten patients had diabetes mellitus, and all had renal insufficiency, conditions that are independently associated with decreased peripheral T3 production. The TT3/TT4 ratio in our patients with nephrotic syndrome and normal glomerular filtration rates without other complicating illnesses were normal<sup>26</sup> suggesting that these patients may not have impaired T3 production. The definitive answer to this question requires the measurement of T3 production rates in these patients. Again, despite the low serum TT3 values the concentrations of TrT3 are normal in patients with nephrotic syndrome and normal glomerular filtration rates.

### Conclusions

Renal diseases result in multiple alterations in serum thyroid hormone levels that may resemble hypothyroidism. Despite such changes, these patients are clinically euthyroid. Thus, thyroid hormone therapy is not indicated unless true hypothyroidism also is present. Knowledge of these changes in serum thyroid hormone indices is essential to diagnose accurately or to exclude the presence of coexisting hyperthyroidism or hypothyroidism. It should be noted that in patients with primary hypothyroidism, in the presence of nonthyroidal illness, the adequacy of levothyroxine therapy may not be accurately reflected by the serum TT4 and free T4 index value and may be better judged on the basis of serum TSH levels.

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