

Consistent Reversible Elevations of Serum Creatinine Levels in Severe Hypothyroidism

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Background: Changes in routine clinical chemical indicators of renal function in the hypothyroid state are not well characterized, and are infrequently discussed in standard internal medicine or subspecialty textbooks.

Patients and Methods: We evaluated 24 consecutive patients with iatrogenic hypothyroidism induced prior to radioiodine scanning for monitoring of thyroid carcinoma. Serum creatinine and thyroid function tests were measured prior to, during, and subsequent to the period of induced hypothyroidism.

Results: Among 29 episodes with paired prior euthyroid and hypothyroid serum creatinine values, the hypothyroid value was greater in 26 (89.7%), and equal in 3 (10.3%), less in none; the mean hypothyroid value was significantly greater (103 vs 76 $\mu\text{mol/L}$ [1.17 vs 0.87 mg/

dL]) ($P < .001$). Among 36 episodes with paired hypothyroid and subsequent euthyroid serum creatinine values, the hypothyroid value was greater in 33 (91.7%), equal in 2 (5.6%), and less in 1 (2.8%); the mean hypothyroid value was again significantly greater (102 vs 75 $\mu\text{mol/L}$ [1.15 vs 0.85 mg/dL]) ($P < .001$). There was no significant difference between prior and subsequent euthyroid serum creatinine values. Serum creatinine values above the stated normal range occurred in 6 of 36 hypothyroid episodes.

Conclusions: There is a consistent and reversible elevation of serum creatinine values in the hypothyroid state. Frankly abnormal serum creatinine levels will occur in some cases.

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CERTAIN EFFECTS of the hypothyroid state on the kidney are well established. Histological changes have been demonstrated in both rats¹ and humans.^{2,3} Physiological effects include changes in water and electrolyte metabolism, notably hyponatremia, and reliable alterations of renal hemodynamics,⁴⁻¹¹ including decrements in renal blood flow, renal plasma flow, glomerular filtration rate (GFR), and single nephron GFR. In 1 study⁴ GFR failed to reach the levels seen in euthyroid controls following the initiation of thyroid hormone replacement therapy, leaving open the possibility that the effect was not fully reversible. The cause of the decreased renal plasma flow and GFR observed is believed to be principally due to the generalized hypodynamic state of the circulatory system in hypothyroidism.¹²

Standard textbooks of internal medicine,^{13,14} nephrology,¹⁵ endocrinology,^{16,17} and thyroidology¹² generally acknowl-

edge the physiological changes mentioned above; however, they either make no mention of serum urea nitrogen and serum creatinine or state that their concentrations are rarely affected. This is said to occur because of a reduced rate of generation of these markers, counterbalancing the decrease in renal function.¹² Despite this, scattered reports of elevated serum creatinine levels in the uncomplicated hypothyroid state^{5,18-21} and reports of severe renal failure resulting from hypothyroidism through the intermediaries of rhabdomyolysis²² and drug toxicity²³ exist.

We recently cared for a patient who developed a serum creatinine level of 159 $\mu\text{mol/L}$ (1.8 mg/dL; normal range, 35-124 $\mu\text{mol/L}$ [0.4-1.4 mg/dL]) associated with normal findings on urinalysis during acute, severe iatrogenic hypothyroidism following levothyroxine sodium treatment withdrawal as part of our protocol for treatment of thyroid carcinoma. The patient had had a normal serum creatinine level of 97 $\mu\text{mol/L}$ (1.1 mg/dL) while in the euthyroid state at the time of thy-

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PATIENTS AND METHODS

The charts of 24 consecutive patients in whom iatrogenic hypothyroidism had been induced in the preceding 2 years for the treatment of thyroid carcinoma were reviewed. Previous documented episodes of induced hypothyroidism in these patients were also analyzed. All patients were withdrawn from levothyroxine therapy 6 weeks prior to the scheduled radioiodine procedure, and were initially receiving a 4-week course of triiodothyronine. During the final 2 weeks of the preparation period no thyroid hormone was administered, resulting in a brief but severe state of hypothyroidism. In this hypothyroid state serum creatinine (H-Cr) values were determined and our routine thyroid function tests were drawn, just prior to administration of iodine 131 for the scan.

We considered a state of severe acute hypothyroidism to have occurred in any patient who had a thyrotropin value greater than 40 mIU/mL (normal range, 0.3-5.0 mIU/mL). This occurred in 20 (6 male, 14 female) of 24 patients on a total of 36 (9 male, 27 female) occasions. Mean age was 37 years (range, 13-76 years). The records were reviewed for documentation of prior serum creatinine (P-Cr) values obtained during the euthyroid state (documented by a simultaneous normal thyrotropin level). Such values were available for 29 of the hypothyroid episodes among 15 patients, the vast majority having been drawn just prior to thyroidectomy. We then prospectively drew blood samples to verify the creatinine and thyrotropin levels for a minimum of 3 months after the reinstatement of levothyroxine replacement (subsequent creatinine [S-Cr]). When this fell outside of our usual clinical practice, informed consent was obtained. If the thyrotropin level was not in the desired range at this time, the replacement dose was adjusted until euthyroidism was achieved, and the corresponding creatinine value was used. The P-Cr and S-Cr values were each compared with H-Cr values, as well as with each other.

Serum creatinine values were determined by coupled enzymatic reaction using an analyzer (Vitros 950 analyzer, Johnson & Johnson, Rochester, NY). Third-generation thyrotropin was determined by 2-site chemiluminometric sandwich immunoassay by automated chemiluminescent system (ACS 180, Chiron Ciba-Corning, Oberlin, Ohio). Statistical analysis was performed by comparing means of the groups by using independent samples *t* tests. All tests were performed using Stata 5.0 (College Station, Tex).

roidectomy, and his creatinine level returned to this same level when a euthyroid state was reestablished following reinitiation of levothyroxine after treatment. This led us to suspect hypothyroidism as the cause of his elevated creatinine level, and prompted us to conduct an analysis of our patients treated in this manner to assess for similar changes, and to determine whether these changes were consistent or sporadic, and if they were fully reversible.

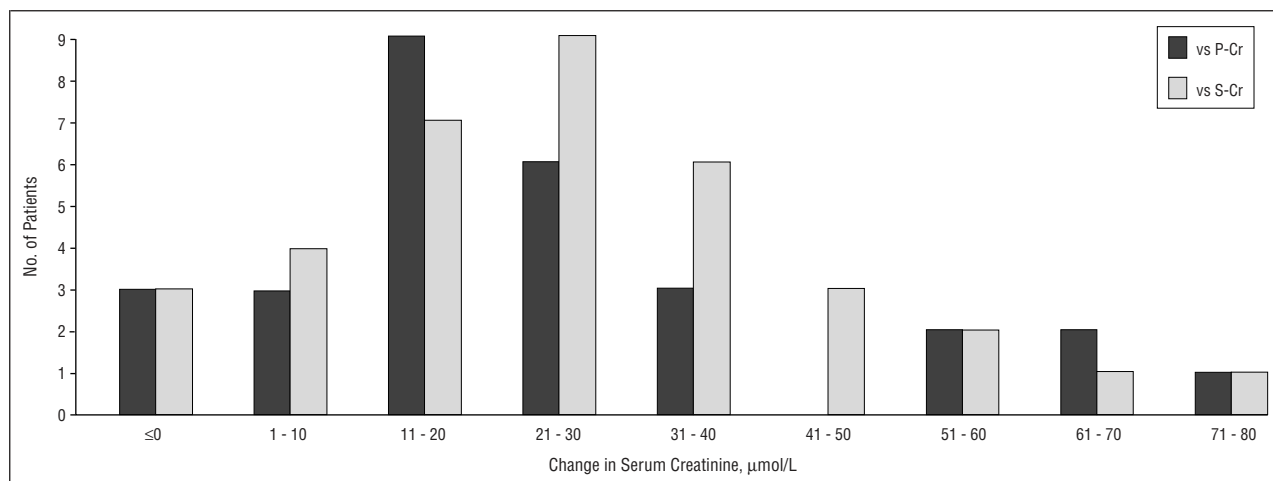
Among 29 episodes of hypothyroidism in the subgroup of 15 patients with paired hypothyroid and prior euthyroid creatinine values, the hypothyroid creatinine value was greater in 26 episodes (89.7%), the same in 3 (10.3%), and less in none. The distribution of the change in serum creatinine values is depicted in the **Figure**. Mean hypothyroid creatinine values were significantly greater than mean prior euthyroid creatinine values at 103 vs 76 $\mu\text{mol/L}$ (1.17 vs 0.87 mg/dL), respectively ($P < .001$), a 26- $\mu\text{mol/L}$ (0.3-mg/dL) or 34.4% increase.

Among 36 episodes of hypothyroidism in the 20 patients with paired hypothyroid and S-Cr values, the hypothyroid creatinine value was greater in 33 (91.7%), the same in 2 (5.6%), and less in 1 (2.8%). The distribution of the change in serum creatinine values is depicted in the **Figure**. Mean hypothyroid creatinine levels were significantly greater than mean S-Cr at 102 vs 75 $\mu\text{mol/L}$ (1.15 vs 0.85-mg/dL), respectively ($P < .001$), a 26- $\mu\text{mol/L}$ (0.3-mg/dL) or 35.2% difference.

Among 29 documented episodes of hypothyroidism in 15 patients with P-Cr, H-Cr, and S-Cr values, a comparison of mean P-Cr and S-Cr values showed no significant difference (77.0 vs 77.6 $\mu\text{mol/L}$ [0.87 vs 0.88 mg/dL], respectively; $P = .88$).

Five of 6 male patients developed H-Cr values above the stated normal range for our laboratory in a total of 6 (66.7%) of 9 hypothyroid episodes (**Table**), while none of 14 female patients developed such values in any of 27 hypothyroid episodes. No patient had an abnormal creatinine value at either of the euthyroid draws. Male patients had higher mean euthyroid creatinine values than female patients both prior to (91 vs 72 $\mu\text{mol/L}$ [1.03 vs 0.81 mg/dL]; $P < .001$) and subsequent to (99 vs 67 $\mu\text{mol/L}$ [1.12 vs 0.76 mg/dL]; $P < .001$) the hypothyroid episode. Male patients also had higher mean H-Cr values than female patients (137 vs 90 $\mu\text{mol/L}$ [1.55 vs 1.02 mg/dL], $P < .001$ when paired with P-Cr, and 138 vs 90 $\mu\text{mol/L}$ [1.56 vs 1.02 mg/dL], $P < .001$ when paired with S-Cr), and higher mean absolute increases in creatinine levels during the hypothyroid state (47 vs 17 $\mu\text{mol/L}$ [0.53 vs 0.20 mg/dL], $P < .001$ when paired with P-Cr, and 38 vs 23 $\mu\text{mol/L}$ [0.43 vs 0.26 mg/dL], $P = .02$ when paired with S-Cr).

Considering whether creatine kinase levels, as a marker of increased muscle breakdown, related to the changes of creatinine levels seen in the hypothyroid state, creatine kinase levels were drawn on a total of 17 hypothyroid occasions. Levels above the stated normal range were obtained in 6 of the 17 draws. Highest creatine kinase value obtained was 667 IU/L (normal range, 30-210 IU/L). No patient developed evidence of clinically significant rhabdomyolysis. Five of the 6 patients with elevated creatine kinase values had negative findings from urinalyses, and the last was a female patient with a "large" reaction for hemoglobin, 11 to 20 red blood cells and a negative test result for protein (a positive reaction for hemoglobin in the absence of red blood cells would be suggestive of rhabdomyolysis). The degree of H-Cr elevation was not significantly different between patients with normal and high creatine kinase levels (33 vs 34 $\mu\text{mol/L}$ [0.37 vs 0.38 mg/dL], respectively; $P = .98$).



Distribution of change in serum creatinine levels between thyroidal states. Each 10- $\mu\text{mol/L}$ increment corresponds to 0.1 mg/dL (original units). Darker bars compare hypothyroid and prior euthyroid (P-Cr) creatinine levels; lighter bars, hypothyroid and subsequent euthyroid (S-Cr) creatinine levels.

Patients With Abnormal Hypothyroid Serum Creatinine Values*

Patient	P-Cr, $\mu\text{mol/L}$ (mg/dL)	H-Cr, $\mu\text{mol/L}$ (mg/dL)	S-Cr, $\mu\text{mol/L}$ (mg/dL)
1A	79 (0.9)	141 (1.6)	97 (1.1)
1B	79 (0.9)	132 (1.5)	97 (1.1)
2	106 (1.2)	177 (2.0)	106 (1.2)
3	97 (1.1)	159 (1.8)	97 (1.1)
4	106 (1.2)	159 (1.8)	106 (1.2)
5	NA	141 (1.6)	97 (1.1)

*Normal range for serum creatinine is 35 to 124 $\mu\text{mol/L}$. P-Cr indicates prior euthyroid serum creatinine; H-Cr, hypothyroid serum creatinine; S-Cr, subsequent euthyroid serum creatinine; and NA, not available.

Considering whether intrinsic renal disease related to the changes of creatinine levels observed, urinalysis was performed in 34 patients during the hypothyroid state. Twenty-two were normal, and 12 had mild abnormalities, 8 showed various numbers of red blood cells and/or a positive reaction for hemoglobin, 3 minimal protein, and 2 both. The degree of H-Cr rise was not significantly different between patients with normal or mildly abnormal urinalysis findings (27 vs 26 $\mu\text{mol/L}$ [0.31 vs 0.29 mg/dL], respectively; $P = .71$).

COMMENT

Despite its absence from standard reference texts,¹²⁻¹⁷ there are several reports relating elevated serum creatinine levels to the uncomplicated hypothyroid state. These include a cross-sectional study comparing 8 hypothyroid individuals with euthyroid controls,¹⁸ 2 studies of 10 and 41 patients with primary hypothyroidism before and after replacement therapy,^{5,19} 2 case reports of a total of 3 adults and 1 child,^{20,21} and a study²⁴ comparing euthyroid with hypothyroid radioiodine scans that alludes to creatinine levels. Taken together, these studies demonstrate that serum creatinine levels are elevated in the hypothyroid state, at times to frankly abnormal levels, and one of these studies clearly relates this finding to a re-

duced GFR.⁵ However, the literature to date can make no statement as to the length of time needed to develop the abnormal creatinine level, nor does it explore renal function prior to the development of the hypothyroid state, leaving open the possibility that the condition is not fully reversible.

The present study compared creatinine values obtained after a 2-week period of complete thyroid hormonal deprivation with values obtained both previously and subsequently during states of euthyroidism in the same patients. We found that serum creatinine levels were approximately 35% higher in the hypothyroid state. Furthermore, by showing that creatinine levels were higher in the hypothyroid state in about 90% of paired values, we have shown that this is a consistent and predictable occurrence, as opposed to one that occurs randomly, or only in a small subset¹² of patients. The rise in creatinine levels did not relate to abnormalities in creatine kinase levels or on urinalysis, suggesting that neither hypothyroid myopathy nor intrinsic renal disease contributed to the changes seen. As demonstrated in the subgroup of patients with P-Cr, H-Cr, and S-Cr values, a comparison of P-Cr and S-Cr values showed no difference, indicating that the elevated creatinine values of hypothyroidism are indeed fully reversible on full replacement of thyroxine. We have also shown that only a very short period of hypothyroidism is required to develop the elevated creatinine level, which is in keeping with animal studies previously mentioned.¹ Although our study does not address the possibility that the serum creatinine level changes of acute hypothyroidism are transient, the similarity of the magnitude of the changes noted in our study to those seen in the above-mentioned studies of the chronic hypothyroid state suggest that this is not the case. Last, and potentially most important from the perspective of the clinician, we have added 5 patients to the already growing list of those with frankly abnormal creatinine values due to hypothyroidism, confirming that it is truly a cause of mild acute renal failure. That all 5 of these patients in our study were male is interesting, and likely relates to the higher baseline creatinine values in these patients presumably due to higher

muscle masses. However, abnormal values have also been reported in females.⁵

The consistency of the elevation in creatinine levels in our study and others^{5,19} argues against the previously held notion of a net unchanged creatinine value due to a balance between the decrease in renal clearance and a decrease in creatinine generation.¹² In fact, in the only report on creatinine generation found,¹⁸ it was not significantly different between the hypothyroid patients and the euthyroid controls, and it actually fell slightly in the only patient in whom it was measured both before and after thyroid hormone replacement. Indeed, it is possible that in a small minority of cases creatinine generation actually increases enough to be the primary cause of the increased serum creatinine levels.²⁰

In conclusion, this study confirms that the hypothyroid state is associated with a consistent elevation in the serum creatinine level, presumably due to a decrease in the GFR, and demonstrates that it is a reversible change that develops rapidly. Knowledge of the association between hypothyroidism and an elevated creatinine level is important for the clinician in that it would prevent an otherwise unexplained result in the hypothyroid patient from leading to unnecessary investigation, cost, and worry. Conversely, it should also lead the clinician to consider an evaluation of thyroid function in the workup of the patient with a modest elevation of creatinine level whose thyroid status is undetermined. The implications of changes in GFR in the hypothyroid state in relation to potential alterations in drug therapy dosing is yet to be fully explored. The association between hypothyroidism and an elevated serum creatinine level is not included in standard internal medicine or subspecialty textbooks today, but probably should be in the future.

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