

# Elevated Serum Creatinine Level in Thyroid Cancer Patients Undergoing Withdrawal of Thyroxine Therapy for Radioiodine Scan/Treatment

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Chronic hypothyroidism is known to cause a significant reversible decrease in glomerular filtration rate (GFR). However, the effect on GFR of acute hypothyroidism, routinely induced in thyroid cancer patients in preparation for radioiodine scan/treatment, is not known. We studied the prevalence of abnormal serum creatinine level and the degree of its increase in hypothyroid patients with thyroid cancer four weeks after the withdrawal of thyroxine therapy. Creatinine level was measured in 116 patients on 191 hypothyroid episodes and in 56/116 and 18/116 patients while euthyroid or mildly hyperthyroid respectively. Abnormal creatinine level was significantly more prevalent in the hypothyroid state (34.5% vs 4% in the euthyroid or mildly hyperthyroid states) and significantly more common in males (50% vs 29% in females), in patients  $\geq$  31 years old (48% vs 26% in older patients) and in patients with a TSH level  $>150$  mU/L (55% vs 30% with TSH  $\leq$  150 mU/L). Analyzing data on females only or including all hypothyroid episodes did not significantly alter the results. Further, compared to patients with normal creatinine level, patients with abnormal creatinine levels were significantly younger (in the whole group, mean age 35.1 vs 42.5 years; in the subgroup of patients with a TSH level  $> 150$  mU/L, 29.8 vs 41.4 years; in females, 28.3 vs 42.5 years) and there was a significant negative association between the presence of abnormal creatinine levels and different age groups. Compared to levels obtained in the euthyroid or mild hyperthyroid states, creatinine levels increased in the hypothyroid state on average 32% (23  $\mu$ M/L,  $P=0.0001$ ) with 24% of patients having  $\geq$ 50% increase. Elevated serum creatinine levels are rather common in thyroid cancer patients undergoing temporary withdrawal of thyroxine treatment and more so in males, younger patients or in association with higher TSH levels. Since the clearance of iodine is linearly related to GFR, our study suggests that in the setting of hypothyroidism, the bioavailability of a given dose of radioiodine may have significant individual variation. *Ann Saudi Med* 1995;15(4):

Long-standing hypothyroidism can cause significant reversible changes in renal function such as a decrease in sodium resorption in the proximal tubules, an impairment in the concentrating and diluting capacities of the distal tubules, a decrease in urinary urate excretion, and a decrease in renal blood flow and glomerular filtration rate (GFR).<sup>1-4</sup> In experimental animals, surgical or drug-induced hypothyroidism of a few weeks' duration has also been shown to result in a decrease in GFR.<sup>5-7</sup> However, the effect of hypothyroidism of short duration on GFR or serum creatinine level in humans has not been well documented.

We retrospectively studied the prevalence of abnormally elevated serum creatinine level and the degree of its increase in patients who had undergone thyroidectomy for differentiated thyroid cancer and in whom thyroxine therapy was withheld for four weeks in preparation for radioiodine scanning/treatment.

## Patients and Methods

The medical records of all thyroid cancer patients who had radioiodine thyroid scans (diagnostic or postablation) at King Faisal Specialist Hospital and Research Centre during the three months before the start of the study were reviewed. Creatinine levels had been routinely determined in these patients. All patients who had serum creatinine measurement while being hypothyroid, as evidenced by a simultaneous TSH level of  $\geq 30$  mU/L, were included in the study. All patients had I<sup>131</sup> and/or surgical thyroid ablation and were on thyroxine therapy until four weeks before the determination of creatinine levels. Out of 116 patients included in the study, 74 had, in addition, serum

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(n=16, TSH <0.2 mU/L, free T4=16.35 [mean=20.6] pmol/L). The mild hyperthyroid state was the result of treatment with a suppressive dose of thyroxine (0.15 to 0.2 mg/day), whereas the euthyroid state was the result of suboptimal suppression or was present before thyroidectomy. The euthyroid/mild hyperthyroid creatinine measurements followed 45 hypothyroid creatinine measurements and preceded 87. The mean age of the patients ( $\pm$ SD) was  $40 \pm 16$  with a range of six to 89 years. There were 86 females and 30 males. Forty-four patients (seven males and 37 females) were  $\leq 31$  years old, whereas 72 (23 males and 49 females) were  $>31$  years of age. In the first hypothyroid episode, 96 patients had a TSH  $\leq 150$  mU/L, whereas 20 had a TSH  $>150$  mU/L. Each of the 116 patients had one to four hypothyroid episodes (total = 191). Considering all hypothyroid episodes, mean TSH level ( $\pm$  SD) was  $125 \pm 94$  with a range of 30 to 360 mU/L. Sixty-five hypothyroid episodes occurred in patients  $\leq 31$  years old, 126 in patients  $>31$  years old, 137 in females, 54 in males, 148 with a TSH  $\leq 150$  and 43 with a TSH of  $>150$  mU/L. One hundred and twelve patients had papillary, three had follicular and one had Hurthle cell thyroid cancer. Eight patients had essential hypertension, nine had diabetes mellitus, and two had both; all were on treatment with good to fair control; in this subgroup of patients (with hypertension, diabetes or both) there were nine abnormal creatinine levels in 28 hypothyroid episodes (32%). No patient was known to have renal disease except for three who had mildly elevated basal creatinine levels. Routine urinalysis, when available, was normal in all patients.

**TSH and free T4 assays:** TSH and free T4 levels were determined using Amerlite TSH assay or Amerlite free thyroxine assay kits obtained from Amersham, UK. Both

TABLE 1. Upper normal values for creatinine ( $\mu$ m/L) level according to age and sex.<sup>a</sup>

	Age group (years)					
	4-8	8-11	11-13	13-31	31-61	>61
Males	71	75	82	105	115	120
Females	62	65	76	90	100	100

a=adapted from reference 8 and confirmed in our Saudi population.

TABLE 2. The prevalence of elevated creatinine level in patients with acute hypothyroidism according to age, sex, creatinine level in a previous hypothyroid episode or TSH level.

	Prevalence of Abnormal Creatinine Level (%)							
	Age (years)		Sex		Creatinine level in a previous episode		TSH (mU/L)	
	$\leq 31$	$> 31$	M	F	Abnormal	Normal	$> 150$	$\leq 150$
A	48	26	50	29	—	—	55	30
B	42	28	44	28	40	20	47	28
C	49	14	—	—	—	—	50	25

to manufacturer's recommendation. The normal ranges for TSH and free T4 are 0.2 to 5.0 mU/L and 10 to 25 pmol/L, respectively (using Saudi male blood donors). The intra- and interassay coefficients of variation (CV) are 4% for TSH and 5.5% for free T4.

**Creatinine, urea and urate assays:** Creatinine, urea and urate levels were determined on Hitachi 737 or 717 analyzer, Boehringer Mannheim GmbH, Mannheim, Germany, according to manual recommendations. Creatinine assay uses Jaffe method (kinetic) without deproteinization. Urate assay is an enzymatic colorimetric test, whereas urea assay is a kinetic UV test. Values were considered abnormal if they fell above the normal range (age and sex adjusted) that was established in our clinical laboratory (adopted from published data<sup>8</sup> and confirmed in our Saudi population). Upper normal values for creatinine for different age groups are shown in Table 1. The intra- and interassay CV for creatinine, urea and urate are 3.5 and 3.6, 2.8 and 3.6, and 2.1 and 2.5 respectively.

**Statistical analysis:** Data are summarized as means (SD) for continuous variables and as proportions or percentages for categorical variables. The statistical comparisons were made using chi-square test, paired t-test and unpaired t-test or their nonparametric counterparts. Standard statistical packages, i.e., SAS and StatGraphics were used to carry out the analysis.

## Results

**The prevalence of abnormal creatinine level and its correlation with age, sex or TSH level:** In the first hypothyroid episode, serum creatinine levels were elevated above the normal range of age- and sex-matched controls in 40/116 (34.5%) patients. For comparison, only 3/74 patients (4%) of the same cohort had abnormal creatinine levels in the euthyroid/mild hyperthyroid states ( $P < 0.001$ ). In 19 patients with abnormal creatinine levels during hypothyroidism, creatinine levels were available in the following euthyroid/mild hyperthyroid states; all became normal, indicating that this abnormality is reversible.

respectively.

As shown in A of Table 2, the prevalence of abnormal creatinine levels was significantly higher in patients  $\leq 31$  (21/44) years compared to older patients (19/72), in males (15/30) compared to females (25/86), and in patients with a TSH  $>150$  (11/20) compared to patients with a TSH  $\leq 150$  mU/L (29/96). Further, the mean age of patients with abnormal creatinine levels was lower compared to patients with normal creatinine levels ( $35.1 \pm 15$  vs  $42.5 \pm 15.7$  years,  $P = 0.02$ ). Furthermore, as shown in Figure 1, there was significant negative association between the presence of abnormal creatinine level and different age groups. Mean TSH level in patients with abnormal creatinine level was higher than that in patients with normal creatinine level but did not reach statistical significance ( $134 \pm 93$  vs  $110 \pm 102$  mU/L,  $P = 0.2$ ).

Considering all hypothyroid episodes, abnormal creatinine level was present in 62/191 (32%) episodes. As shown in B of Table 2, this was also more frequent in males (24/54 vs 38/137 in females), younger patients (27/65 vs 35/126 in patients  $> 31$  years old) and in association with a TSH  $>150$  mU/L (20/43 vs 42/148 with a TSH  $\leq 150$ ). In addition, having an abnormal creatinine level during the first hypothyroid episode predicted the presence of an abnormal creatinine level in subsequent hypothyroid episodes (12/30 vs 9/45 with normal creatinine level in the first hypothyroid episode). Further, compared to hypothyroid episodes associated with normal creatinine level, hypothyroid episodes associated with abnormal creatinine level had higher mean TSH level ( $145 \pm 93$  vs  $116 \pm 93$  mU/L,  $P = 0.05$ ).

**Subgroup analysis:** To determine whether age, sex and TSH level are independent variables, the data were subjected to subgroup analysis whenever the number of patients was adequate.

**Sex:** In female patients, the overall prevalence of abnormal creatinine level in the hypothyroid state was 29% (25/86). Age and TSH level remained good predictors of abnormal creatinine level (C of Table 2). Further, the mean age of females with abnormal creatinine level was lower than that of females with normal creatinine level ( $28.3 \pm 8$  vs  $42.5 \pm 15.5$  years,  $P = 0.0001$ ). Mean TSH level was also higher in females with abnormal creatinine level ( $141 \pm 108$  vs  $103 \pm 86$ ,  $P = 0.09$ ).

**Age:** In patients  $>31$  years old, abnormal creatinine level was more frequent in males compared to females (52% vs 14%,  $P = 0.001$ ) and in the subgroup of patients with a TSH level  $>150$  compared to the subgroup with a TSH  $\leq 150$  mU/L (42% vs 23%,  $P = 0.2$ ).

**TSH Level:** In patients with a TSH level  $\leq 150$  mU/L, abnormal creatinine level was also more frequent in males compared to females (46% vs 25%,  $P = 0.05$ ) and in patients  $\leq 31$  years old compared to those  $>31$  years old (42% vs 23%,  $P = 0.06$ ). In patients ( $n=20$ ) with a TSH level  $> 150$  mU/L, the mean age of patients with abnormal

normal creatinine level ( $29.8 \pm 9.6$  vs  $41.4 \pm 13.6$ ,  $P = 0.04$ ).

**Comparison between creatinine levels in the hypothyroid and the euthyroid/mild hyperthyroid state:** Means of creatinine levels in the euthyroid ( $n=56$ ) and mild hypothyroid ( $n=18$ ) states were not significantly different (69.9 and 67.1  $\mu\text{mol/L}$  respectively). Thus the two groups were combined for the following analysis: mean ( $\pm\text{SD}$ ) creatinine level was  $96.3 \pm 24$  in the first hypothyroid episode compared to  $73 \pm 18.3$   $\mu\text{mol/L}$  in the euthyroid/mild hypothyroid state ( $P = 0.0001$  using the paired t-test). Figure 2 depicts creatinine levels in the first hypothyroid episode and in the euthyroid/mild hyperthyroid state in three subgroups: males 32 to 61 years old, females

FIGURE 1. The prevalence of abnormal creatinine level in acute hypothyroidism according to age. The first hypothyroid episodes in 116 patients are presented. The number (n) of patients in each subgroup is indicated. The difference between age groups is statistically significant using the chi-square test ( $P=0.04$ ).

FIGURE 2. Comparison of serum creatinine levels in the euthyroid and hypothyroid states. Bars represent mean ( $\pm\text{SD}$ ). The euthyroid group included patients with mild hyperthyroidism (see text). Patients were divided into subgroups according to sex and age (years). The number (n) of patients in each subgroup is indicated. The difference between the euthyroid and

mean ( $\pm$  SD) difference between the two states was  $27.2 \pm 15.1$ ,  $26.7 \pm 17.6$ , and  $23.3 \pm 12.3$  in the three subgroups, respectively ( $P = 0.0001$  using the paired t-test). Further, there was <sup>3</sup>10% increase in creatinine level in 72% of patients, <sup>3</sup>25% in 58%, <sup>3</sup>50% in 24%, <sup>3</sup>75% in 7% and <sup>3</sup>100% in 2%.

*Urea and urate levels:* Urea and urate levels were available in 86 and 44 hypothyroid episodes respectively. Only seven patients (8%) had urea levels above the normal range of age- and sex-matched controls. Five out of seven patients with abnormal urea level also had abnormal creatinine levels. No patient had an abnormal urate level.

## Discussion

This study reveals several interesting observations. First, severe short-lived hypothyroidism caused by the withdrawal of thyroxine therapy for four weeks in previously thyroidectomized patients is associated with a substantial increase in serum creatinine levels. Abnormal creatinine levels were present in 34.5% of patients in the hypothyroid state compared to 4% in the euthyroid/mild hyperthyroid state. Further, 24% of patients had at least a 50% increase in creatinine levels in the hypothyroid state. That hypothyroidism is the cause of abnormal creatinine levels is suggested by the fact that creatinine levels decreased after resumption of thyroxine therapy and that the prevalence of abnormal creatinine levels correlated with TSH levels. Second, abnormal creatinine levels are 1.5 to 2 times more common in males in association with a TSH level  $>150$  mU/L or in patients  $\geq 31$  years old. Third, abnormal serum urea levels are much less common than abnormal creatinine levels, whereas uric acid levels are normal in severe short-lived hypothyroidism.

The observed increase in creatinine levels is most likely due to decreased GFR. However, since creatinine clearance and CPK levels were not measured, we cannot exclude the possibility that the observed increase in creatinine levels was due in part to some degree of myopathy and increased release of creatinine from muscles. This may explain the fact that only 8% of the patients had raised urea levels and that increased creatinine levels were more prevalent in younger people and in males. However, increased creatinine release from muscles has not been reported before in hypothyroidism. On the other hand, it is well established that long-standing hypothyroidism in humans can cause several changes in renal function including a decrease in GFR.<sup>2,4</sup> GFR values in myxedematous patients are on average one-third lower than the values in euthyroid individuals.<sup>2</sup> This decrement in GFR is readily reversible upon correction of thyroid

hormone deficiency.<sup>14</sup> Myxedematous patients exhibit decreased Na<sup>+</sup>-K-ATPase activity in the proximal tubules<sup>6</sup> and decreased GFR that can be prevented by the co-administration of thyroxine.<sup>5,6</sup> Similar changes in GFR were observed in dogs four to six weeks after thyroidectomy.<sup>7</sup> Further, lithium-caused hypothyroidism was associated with decreased GFR and elevated creatinine levels that were normalized by thyroxine treatment.<sup>3</sup> The pathogenesis of decreased GFR in hypothyroidism is not completely clear. It may be related to decreased cardiac output,<sup>2</sup> structural glomerular alterations<sup>6,7</sup> and/or to decreased levels of plasma atrial natriuretic factor (ANF).<sup>7,9,10</sup>

The influence of age or sex on GFR decrement associated with long-standing hypothyroidism has not been well documented. However, of note is the fact that although GFR is in general 15% higher in males compared to females,<sup>11</sup> compiling data from several studies,<sup>2,12,13</sup> GFR in 33 hypothyroid females was 69 compared to 69.4 mL/min in 17 hypothyroid males. Further, after thyroid replacement therapy, GFR increased by 41% in a 26-year-old male compared to 19% in a 60-year-old male.<sup>14</sup> Although subgroup analysis was somewhat limited in our study because of the small number of patients in some of the subgroups, it suggests that age, sex and TSH levels are independent variables.

Decreased urinary urate excretion in myxedematous patients causes frank hyperuricemia in men and postmenopausal women, which is reversed by thyroid hormone replacement.<sup>1</sup> The reason for not detecting abnormal urate level in our patients is not clear, but it could be due to different patient population or to a shorter duration of hypothyroidism.

Our findings, if confirmed in a prospective study using direct measurement of GFR, may have an important implication on the interpretation of radioiodine scans and on the estimation of the treatment dose of I<sup>131</sup> for differentiated thyroid cancer. Since urinary excretion of inorganic iodide (its principal clearance route) is linearly related to GFR<sup>14,15</sup> and since the degree of GFR impairment (as reflected by serum creatinine levels) is variable among hypothyroid patients, the availability of a given dose of radioiodine to residual thyroid tissue/thyroid metastases as well as to nontargeted tissues may have significant individual variation. This could result in a relative overestimation of the amount of residual thyroid tissue in patients with decreased GFR and delayed I<sup>131</sup> clearance. In addition, delayed clearance of blood background activity of I<sup>131</sup> may adversely affect the target-to-nontarget ratio of activity and the optimal time of performing the scan. In general, I<sup>131</sup> treatment regimens of thyroid cancer are empirical and the degree of the potential increase in the bioavailability of I<sup>131</sup> in some hypothyroid patients may not significantly affect the estimation of I<sup>131</sup> dose. However,

the efficacy of various  $I^{-}$  treatment regimens. Finally, an elevated creatinine level in the setting of acute hypothyroidism is most likely transient and further work-up may not be warranted.

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