

# Reviewing Biochemical Kidney Parameters in Female Patients with Thyroid Disarrays under Drug Therapy

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## ABSTRACT

**Aim:** To explore the outcome of thyroid disorders on the kidney and the impact of thyroid disorder treatment on the renal functions.

**Methods:** Hospital-based a retrospective review of the medical records was conducted including the patients attending the internal medicine outpatient department, Mansoura University Hospital, Mansoura Governorate, Egypt. A total of 480 individuals, euthyroid group (250) and diseased group (230) with thyroid dysfunction under drug therapy, were randomly selected from patients attending the outpatient clinic in the hospital. Serum thyroid hormones and renal functions were evaluated.

**Results:** It was observed that serum creatinine was increased in the hypothyroid group in contrast to other groups. But it decreased in the hyperthyroid group. There is a moderate negative correlation between T3 and T4 as compared with serum creatinine. Blood urea was increased in hypothyroid and hyperthyroid groups as compared with the euthyroid group. It reached its highest value in the hyperthyroid group. In the present work, it was noticed serum creatinine started to decrease with the progress of treatment till it becomes more or less similar to the euthyroid group after 2 years of treatment in hypothyroid and after 6 months in the hyperthyroid group.

**Conclusion:** serum creatinine and blood urea show significant alterations in patients with abnormal thyroid status. Early investigation of renal biochemical abnormalities can increase the opportunity of restoring normal kidney function by the treatment of thyroid dysfunction.

**Keywords:** Thyroid gland, hyperthyroidism, hypothyroidism, creatinine, urea

## INTRODUCTION

The thyroid is the first endocrine gland to evolve in the embryo and is of endodermal origin. The thyroid gland secretes thyroxine hormone which contains iodine. Thyroxine has effects on all organs of the body and its secretion is regulated by the pituitary gland.<sup>1</sup>

Thyroid disorders are usually classified as hypothyroidism, and hyperthyroidism, according to serum T3 and T4 concentration. This thyroid function disarray may be accompanied by various complications, comprising kidney functions derangement and electrolyte imbalance<sup>2,3</sup>.

The kidneys are the organs through which waste from the blood is filtered. They are also concerned with blood pressure regulation, electrolyte balance, and red blood cell formation.<sup>4</sup> Thyroid hormone influences the renin-angiotensin system and renal tubular function and is accompanied by circulatory changes affecting renal blood flow.<sup>5</sup> Conversely, the kidney is implicated in the metabolism and clearance of thyroid hormones and a target organ of some of the actions of the iodothyronines. Hypothyroidism is linked with increased serum creatinine, and uric acid<sup>6</sup>. On the contrary, hyperthyroidism is associated with a generalized hypermetabolic state<sup>7</sup>. In addition, hyperthyroidism can induce or intensify chronic kidney disease (CKD). On the contrary, hypothyroidism has no role in the evolution of chronic kidney disease except by mild to moderate decline in glomerular filtration rate (GFR).<sup>7</sup> While the outcomes of thyroid

hormones on kidney functions are well established, the impact of management of thyroid disorders on the renal parameters has not been well studied. With this context, the present work was assumed to appraise the renal functions in patients with thyroid derangement and the impact of thyroid disorders therapy on the renal functions.

## SUBJECTS AND METHODS

We conducted a retrospective review of the medical records among the patients attending the internal medicine outpatient department, Mansoura University Hospital, Mansoura Governorate, Egypt. Medical records were retrieved for subjects covering the period between May 1, 2016 and April 31, 2019. Euthyroid group (250) and diseased group (230) with thyroid dysfunction were randomly selected from patients attending the outpatient clinic in the hospital making a total of 480 subjects. Serum thyroid hormones and renal function were evaluated. Follow-up of the chosen patients' files was evaluated after 6 months, 1 year, and 2 years of treatment. The sample size was determined using G\* power (version 3; Franz Faul, University of Kiel, Germany). Calculations based on power of 0.95, an error of 0.05, and effect size of 0.2 were used for a priori power analysis.

**Inclusion Criteria:** Females' ages between 5–70 years old. **Exclusion criteria:** women who have known hypertension, diabetes, receiving contraceptive pills, liver disease, and renal disease.

Data were collected from files including age, weight, height, T3, T4, TSH, serum creatinine, and blood urea levels. Privacy and confidentiality were strictly maintained.

**Statistical Analysis:** The numerical data were collected and computerized using the SPSS program (Statistical Package of Social Science) program, version 21. The association between (renal function tests) and (thyroid hormones) was analyzed using the chi-square to detect the significances between variables of the study. The description of the data was done in the form of mean  $\pm$  standard deviation (SD) for normally distributed quantitative data. One Way ANOVA test was used to test the statistically significant difference between groups. Finally, the Receiver Operating Characteristic (ROC) curve was analyzed to assess the biochemical markers of kidney function predictability to classify hypothyroidism from euthyroid patients and hyperthyroidism from euthyroid patients.

Significance difference was considered when the P-value was  $\leq 0.05$  at a confidence of interval 95 %.

## RESULTS

**Demographic data of the study group:** A total of 480 female subjects during the duration of study were screened. 250 were euthyroid, 130 were diagnosed as hypothyroidism and 100 were diagnosed as hyperthyroidism. None of the subjects included had evidence of kidney disease.

Table (1) showed the distribution of study samples according to age group. In hypothyroidism, the percentage (46.2%) was the highest and the same in the age group that ranges between (26-45) years & (46-70) years while the lowest (7.7%) for the age group (5-25) years. On the other hand, in the age group that ranges between (26-45) years, there were (50%) patients which represent the highest percentage while the lowest percentage was (10%) for the age group (46-70) years in hyperthyroidism group.

Table (1) showed the distribution of study samples according to body mass index (BMI). In hypothyroidism, the percentage (46.2%) was the highest in the obese group and was higher than that in the hyperthyroid group followed by normal (30.8%) and finally the overweight (23.1%). In hyperthyroidism, the highest percentage were overweight and obese (40%) while the lowest was normal (20%).

**Correlation between level of thyroid hormones and kidney function parameters:** Table (2) showed a decrease in serum T3 and T4 in hypothyroidism as compared with the euthyroid and hyperthyroid group. The decrease in T4 especially was significant in this group as compared with other groups ( $P < 0.05$ ). While in the hyperthyroid group, T3 and T4 increased as compared with other groups. The increase in T4 especially was significant in this group in contrast to with hypothyroid group ( $P < 0.05$ ).

On the other hand, it was observed a marked increase in TSH in both hypothyroid and hyperthyroid groups as compared with both reference range and euthyroid group, and this increase was highly significant ( $P < 0.001$ ) (Table 2). There was a strong negative correlation between TSH as compared with T3 and T4 especially T4 (Table 3) in hypothyroidism. While in the hyperthyroid group, this correlation was moderately positive

in the case of T3 and weak negative in the case of T4. (Table 4)

Serum creatinine was increased in the hypothyroid group as compared with other groups. But it decreased in the hyperthyroid group (Table 2). There is a moderate negative correlation between T3 and T4 as compared with serum creatinine i.e. decrease in T3 and T4 is accompanied by an increase in serum creatinine in case of hypothyroidism (Table 3) while the increase in serum T3 and T4 is accompanied by a decrease in serum creatinine in case of hyperthyroidism (Table 4).

Blood urea was increased in hypothyroid and hyperthyroid groups as compared with the euthyroid group. It reached its highest value in the hyperthyroid group (Table 2). There is a weak negative correlation between T3 and T4 as compared with blood urea in hypothyroidism i.e. decrease in T3 and T4 is accompanied by an increase in blood urea in case of hypothyroidism (Table 3) while positive correlation in hyperthyroidism i.e. increase in serum T3 and T4 is accompanied by an increase in blood urea (Table 4)

**Correlation between thyroid dysfunction and kidney function tests relative to disease duration:** Table (5) illustrates the relation between thyroid dysfunction and kidney function test according to the duration of disease under treatment. It was observed a significant increase in serum creatinine after 6 months in case of hypothyroidism as compared with control ( $0.67 \pm 0.18$  and  $0.65 \pm 0.09$  mg/dl) respectively. After that, serum creatinine started to decrease with the progress of treatment till it becomes more or less similar to the euthyroid group after 2 years of treatment ( $0.65 \pm 0.19$  and  $0.65 \pm 0.09$  mg/dl) respectively. On the other hand, the blood urea was gradually increased with the period of treatment but this increase was non-significant. It was observed weak negative correlation between serum creatinine and period of treatment in case of hypothyroidism, i.e. with the progression of the duration of treatment; there is a decrease in serum creatinine (Table 6).

In the case of hyperthyroidism, it was observed highly significant ( $P < 0.001$ ) decrease in serum creatinine after 6 months as compared with control ( $0.18 \pm 0.10$  and  $0.65 \pm 0.09$  mg/dl) respectively. After that, serum creatinine started to increase with the progress of treatment reaching its highest level after 1 year ( $0.77 \pm 0.21$  mg/dl) (become more than the euthyroid group). On the other hand, the blood urea was gradually increased with the period of treatment but this increase was non-significant (Table 5). It was observed weak positive correlation, i.e. with the progression of the duration of treatment; there is an increase in serum creatinine (Table 6).

In the case of urea, there is an increase in blood urea with the progression of the duration of treatment in both hypothyroidism and hyperthyroid groups (Tables 5, 6).

**ROC-Curve Analysis of Kidney Function Tests:** ROC analyses were implemented to evaluate the thyroid hormones predictability to define the patient's groups (hypothyroidism versus euthyroid) (Fig. 1A). The area under curve (AUC) was 0.55 (95% CI: 0.35–0.75) for T3, 0.27 (95% CI: 0.05–0.48) for T4, and 0.87 for TSH (95% CI: 0.71–1.04). There was significant predictability of TSH for recognizing hypothyroid patients from the euthyroid

group. Figure (1B) evaluates the thyroid hormones predictability to determine the patient's groups (hyperthyroidism versus euthyroid). The AUC was equal to 0.64 (95% CI: 0.44–0.84) for T3, 0.62 (95% CI: 0.38–0.86)

for T4, and 0.60 for TSH (95% CI: 0.30–0.90). There was an insignificant predictability of T3 for recognizing hyperthyroid patients from the euthyroid group.

Table 1: Distribution of study groups based on their ages and body mass index.

Study group		Age Groups			Total	P-value	BMI			Total	P-value
		5-25 years	26-45 years	46-70 years			Normal	Overweight	Obese		
Euthyroid	count	60	150	40	250	0.123 (NS)	110	70	70	250	0.606 (NS)
	%	24%	60%	16%	100%		44.0%	28.0%	28.0%	100%	
Hypothyroidism	count	10	60	60	130		40	30	60	130	
	%	7.7%	46.2%	46.2%	100%		30.8%	23.1%	46.2%	100%	
Hyperthyroidism	count	40	50	10	100		20	40	40	100	
	%	40%	50%	10%	100%		20.0%	40.0%	40.0%	100%	
Total	count	110	260	110	480		170	140	170	480	
	%	22.9%	54.2%	22.9%	100%		35.4%	29.2%	35.4%	100%	

**Weight (kg)**

**-BMI:** Normal weight = 18.5–24.9 Overweight = 25–29.9 Obesity = 30 or greater

**Height (m2)**

Table 2: Comparison of serum T3, T4 and TSH levels in study group and its relation to kidney functions tests (Creatinine and urea).

Variables	Reference range	Study group		
		Euthyroid (n=250)	Hypothyroidism (n=130)	Hyperthyroidism (n=100)
T3 (pmol/L)	3.10-6.80	4.48±0.73 a	4.44±0.78 a	5.12±1.36 a
T4 (pmol/L)	12.00-22.00	16.16±2.43 a	13.72±3.93 b	18.13±4.98 a
TSH (uIU/ml)	0.270 - 4.20	2.29 ± 0.89 a	7.36±4.12 b	8.59±12.50 b
Serum Creatinine (mg/dl)	0.2-1.4	0.65±0.09 a	0.66±0.16 a	0.60±0.23a
Blood urea(mg/dl)	10.0-50.0	28.49±9.35a	29.47±7.23a	30.27±6.73a

The values are the Mean ± SD

Means in a row followed by the same letters are not significantly different (ANOVA-post-hoc comparison, P > 0.05).

Table 3: Correlation between T3, T4 and TSH levels in hypothyroidism and kidney functions tests (Creatinine and urea).

		T3	T4	TSH	Creatinine	Urea
T3	Pearson Correlation Sig. (2-tailed) N	1	.598*	-.289-	-.499-	-.274-
			.031	.339	.082	.365
		130	130	130	130	130
T4		.598*	1	-.684**	-.353-	-.052-
		.031		.010	.237	.866
		130	130	130	130	130
TSH		-.289-	-.684**	1	-.096-	.114
		.339	.010		.754	.712
		130	130	130	130	130
Creatinine		-.499-	-.353-	-.096-	1	.033
		.082	.237	.754		.915
		130	130	130	130	130
Urea		-.274-	-.052-	.114	.033	1
		.365	.866	.712	.915	
		130	130	130	130	130

\*\*Correlation is significant at the 0.01 level (2-tailed). \*. Correlation is significant at the 0.05 level (2-tailed)

Table 4: Correlation between T3, T4 and TSH levels in hyperthyroidism and kidney functions tests (Creatinine and urea).

		T3	T4	TSH	Creatinine	Urea	
T3		1	.296	.504	-.497-	.183	
	Pearson Correlation Sig. (2-tailed) N		.407	.138	.144	.613	
T4		100	100	100	100	100	
			.296	1	-.232-	-.352-	.440
			.407		.520	.319	.203
TSH		100	100	100	100	100	
			.504	-.232-	1	.157	.435
			.138	.520		.664	.209
Creatinine		100	100	100	100	100	
			-.497-	-.352-	.157	1	.362
			.144	.319	.664		.305
Urea		100	100	100	100	100	
			.183	.440	.435	.362	1
			.613	.203	.209	.305	
		100	100	100	100	100	

Table 5: Effect of duration of thyroid dysfunction (under treatment) on T3,T4 and TSH levels in study group and kidney functions tests (Creatinine and urea)

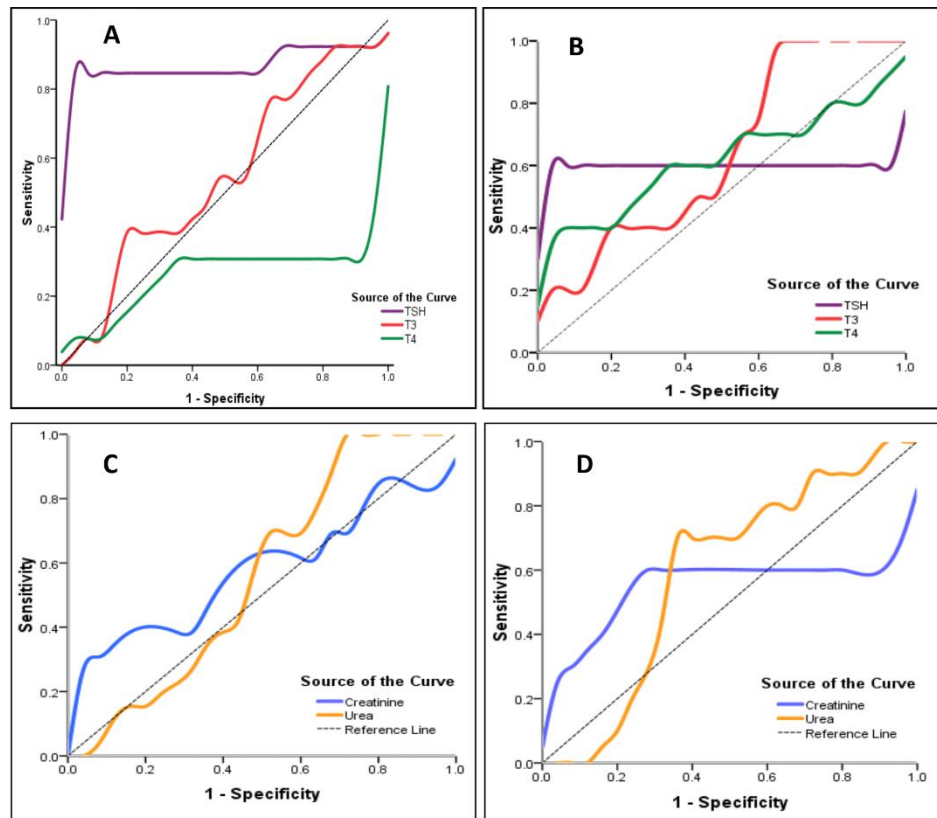
Variables	Reference range	Euthyroid n=250	Hypothyroidism n=130			Hyperthyroidism n=100			P (between groups)
			6 months n=40	1 year n=50	2 years n=40	6 months n=20	1 year n=60	2 years n=20	
T3 (pmol/L)	3.10-6.80	4.48±0.73a	4.37±0.42a	4.77±1.20ac	4.58±0.33ac	4.55±0.50ac	4.39±0.35a	5.91±2.18bc	ns
T4 (pmol/L)	12.00-22.00	16.16±2.43ac	14.07±5.17ad	15.50±3.84ad	11.81±2.36bd	20.41±3.08ac	16.70±5.46a	16.24±7.63ad	ns
TSH (uIU/ml)	0.270 - 4.20	2.29 ± 0.89a	6.27±3.54ac	7.45±5.78ac	8.34±2.80bc	2.42±3.14ac	6.64±1.28ac	20.61±2.88d	0.002
Serum Creatinine (mg/dl)	0.2-1.4	0.65±0.09 a	0.67±0.18bd	0.56±0.07ad	0.65±0.19ab	0.18±0.10c	0.77±0.21b	0.55±0.16ad	<0.0001 Highly significant
Blood urea (mg/dl)	10.0-50.0	28.49±9.35a	28.55±5.61a	29.96±9.14a	29.77±8.05a	24.85±8.84a	31.08±6.75a	33.25±4.60a	ns

The values are the Mean ± Std. Deviation - P value < 0.05 is significant - ns=non-significant - n=number  
Means in a row followed by the same letters are not significantly different (P > 0.05).

Table 6: Correlation between duration of thyroid disorder (under treatment) and kidney functions tests (Creatinine and urea).

Variables	Hypothyroidism (n=130)		Hyperthyroidism (n=100)	
	Pearson Correlation	Sig. (2-tailed)	Pearson Correlation	Sig. (2-tailed)
Creatinine	-.274-	.365	.239	.434
Urea	.069	.822	.507	.210

Figure 1: (A) The ROC analysis for measuring the thyroid hormones cut-off points to differentiate the hypothyroid patients from euthyroid patients. (B) ROC analysis measuring the thyroid hormones to differentiate the hyperthyroid patients from euthyroid patients. (C) ROC analysis for measuring the biochemical factors to differentiate the hypothyroid patients from euthyroid patients.(D) The ROC analysis for measuring the biochemical factors to differentiate the hyperthyroid patients from euthyroid patients.



ROC analyses result for evaluating the biochemical factors predictability to determine the patient's groups (hypothyroidism versus euthyroid) were displayed in (Fig.1C). The area under curve equal to 0.57 for urea (95% CI: 0.38–0.74) and 0.65 for creatinine (95% CI: 0.34–0.77). There was significant predictability of creatinine for

recognizing hypothyroid patients from the euthyroid group. Figure (1D) evaluates the biochemical factors predictability to determine the patient's groups (hyperthyroidism versus euthyroid). The AUC was equal to 0.59 for urea (95% CI: 0.40–0.79), 0.55 for creatinine (95% CI: 0.28–0.82). There

was insignificant predictability of creatinine and uric acid for recognizing hyperthyroid patients from the euthyroid group.

## DISCUSSION

The activity of all body organs and cells is regulated by thyroid hormones. The data discussed in the current study indicates how kidney biochemical markers may be disturbed by changes in the levels of thyroid hormones.

In the present study the inclusion criteria includes females only. The reason for this is that thyroid dysfunction was more frequent in females than males. This was in agreement with previous studies that recorded that hypothyroidism was more frequent in females.<sup>8-10</sup>

Analyzing the distribution of study groups according to their age, it was observed that the highest percentage rate in hypothyroidism (46.2%) was in the patients of age from (26-45) years and (46-70), followed by (7.7%) in patients whom age (5-25) years, the difference between age groups was insignificant ( $P > 0.05$ ). The outcomes of this study were agreed with previous studies that stated the highest percentage of hypothyroidism occurred at the age group (46-70).<sup>8, 9, 11</sup>

The distribution of study samples according to body mass index was studied. In hypothyroidism, the percentage was the highest in the obese group and was higher than that in the hyperthyroid group. Clinical hypothyroidism causes an increase in body weight.<sup>12</sup> In the present work, it was observed in the hyperthyroidism that the highest percentage were overweight and obese (40%) while the lowest was normal (20%). This was in disagreement with previous reports who stated that weight loss is a presenting frequently in hyperthyroidism.<sup>12</sup> But, in our study, there is an important point, which all cases are under treatment for a period of 6 months to 2 years. So, our results were supported by previous studies who reported that although the known catabolic impact of thyroid hormones, almost 40% of their hyperthyroid cohort were overweight at presentation, and by the end of the study 56.2% were overweight and 18.5% obese.<sup>13</sup> Patients treated for hyperthyroidism showed a marked increase in BMI with therapy and continuing gain in weight during follow-up. Hyperthyroidism therapy increases the predictability for obesity, and in previously hyperthyroid patients weight exceeds pre-morbid levels.<sup>14</sup>

The present study showed a highly significant difference between normal and abnormal values of T3, T4  $P < 0.05$  between study groups. T3 and T4 levels significantly decrease in hypothyroidism in contrast to euthyroid and these hormones are increased in hyperthyroidism.<sup>15, 16</sup> The result of this study showed that the TSH level was elevated in hypothyroidism. TSH level was unchanged or elevated in hypothyroidism.<sup>16</sup> Measuring TSH is important for the prediction of hypothyroidism, because of the inverse logarithmic relationship between TSH and T4 meaning that TSH levels will increase long before either T4 or free T4 concentrations falls.<sup>17</sup> It was also noticed in our results increase in TSH in hyperthyroidism with the progress of treatment. But at the beginning of treatment, it was more or less similar to normal. This was in agreement with Jeri *et al.*<sup>15</sup>

In our study, we throw light on the relationship between thyroid dysfunction and kidney function tests. In

hypothyroidism, we noticed that serum creatinine was increased in the hypothyroid group in contrast to other groups and this increase was significant after 6 months of disease. In the case of hypothyroidism, we also observed that blood urea was increased in contrast to the euthyroid group. There is a weak negative correlation between T3 and T4 as compared with blood urea i.e. decrease in T3 and T4 is accompanied by a rise in blood urea in hypothyroidism. Serum urea and serum creatinine significantly increase in hypothyroid patients in comparison with group hyperthyroid & control groups.<sup>18</sup> Previous studies recorded that there was a negative correlation between thyroid hormone and blood urea. The blood urea was likely to increase in hypothyroid cases when T3 levels were low.<sup>19</sup> The hypothesis of nephrogenic histological alteration, namely basement membrane thickening had been established in hypothyroidism in humans and rats.<sup>20</sup> These alterations may cause physiological consequences namely changes in renal hemodynamics, a decrease in renal blood flow (RBF) and GFR, and hence decreased creatinine and uric acid clearance. The exact mechanism of decrease RBF and GFR was overviewed by many authors. The RBF is reduced in hypothyroidism by increased peripheral vascular resistance<sup>21</sup> and decreased reflection of renal vasodilators such as insulin-like growth factor 1 (IGF1) and vascular endothelial growth factor (VEGF).<sup>22-24</sup>

In the present work, it was noticed that serum creatinine started to decrease with the progress of treatment till it becomes more or less similar to the euthyroid group after 2 years of treatment. Previous studies recorded that administration of levothyroxine in hypothyroid patients presenting with hyperuricemia leads to the normalization of TSH, T4, serum uric acid, creatinine, and creatinine clearance values. This data proposed that hypothyroid hyperuricemia could be attributed to a reduction in renal plasma flow and glomerular filtration. Thus the observed decline in serum uric acid level under replacement therapy with levothyroxine could be due to enhancement in its renal excretion.<sup>18, 25, 26</sup>

Another scope in our work was studying the correlation between hyperthyroidism and kidney function tests. Serum creatinine was decreased in the hyperthyroid group which was highly significant ( $P < 0.001$ ) after 6 months as compared with the euthyroid. There is a moderate negative correlation between T3 and T4 as compared with serum creatinine i.e. increase in serum T3 and T4 is accompanied by a decrease in serum creatinine. Blood urea reached its highest value in the hyperthyroid group. Previous reports showed that hyperthyroidism reduces serum creatinine levels slightly and increases serum urea.<sup>10</sup> The mechanisms were explained by many authors. Hyperthyroidism results in increased RBF and GFR by several mechanisms.<sup>27</sup> One of the prerenal aspects, thyroid hormones upsurge the cardiac output by a decrease in systemic vascular resistance in addition to positive chronotropic and inotropic effects.<sup>28</sup> This indirectly leads to an improvement in RBF. The GFR increases by about 18–25% among hyperthyroid patients. The activation of renin-angiotensin-aldosterone system (RAAS) also has a role in increasing GFR. Thyroid hormones stimulate RAAS via different pathways. Serum creatinine is significantly

decreased in hyperthyroid patients, as a result of an increase in GFR and the decrease in whole muscle mass.<sup>29</sup>

In hyperthyroidism, serum creatinine started to increase with the progress of treatment reaching its highest level after 1 year (become more than euthyroid group). It was observed weak positive correlation. The alterations in kidney functions in cases with hypothyroidism or hyperthyroidism are likely to normalize after adjustment of the thyroid dysfunction.<sup>4, 27</sup>

ROC analyses were implemented to assess the thyroid hormones' predictability to define the patient's groups. It was noticed significant predictability of TSH for recognizing hypothyroid patients from the euthyroid group and insignificant predictability of T3 for recognizing hyperthyroid patients from the euthyroid group. Previous reports recorded that there was significant predictability of TSH for recognizing subclinical hypothyroidism from the euthyroid group.<sup>30</sup>

ROC analyses were applied for evaluating the biochemical factors' predictability to determine the patient's groups. There was significant predictability of creatinine for recognizing hypothyroid patients from the euthyroid group. There was insignificant predictability of creatinine and uric acid for recognizing hyperthyroid patients from the euthyroid group. Previous studies stated significant predictability of creatinine and uric acid for recognizing subclinical hypothyroidism from the euthyroid group.<sup>30</sup>

## CONCLUSION

All the outcomes of the current study were promising to determine the complex correlation between the thyroid gland and major organ systems like the kidney. Renal functions comprised serum creatinine and blood urea show significant alterations in patients with abnormal thyroid status. Early investigation of renal biochemical abnormalities in those patients can increase the opportunity of restoring normal kidney function by the treatment of thyroid dysfunction.

**Ethical approval:** The study protocol was carried out in accordance with the rules and regulations approved by the Institutional Research Board (IRB) of Mansoura University (R.19.2.8).

**Disclosure Statement:** No potential conflict of interest

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