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Association of Nephropathy with the Thyroid Profile

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*Corresponding author: <u>Imran.tipu1@gmail.com</u> Abstract

The thyroid gland produces two hormones: thyroxin (T4) and triiodothyronine (T3). The thyroid hormone affects both the kidney morphology and its functions. Kidneys are involved in the metabolism and elimination of the thyroid hormones. The current study was conducted on 100 nephropathy patients, of which 57 were female patients and 43 were male patients. Venous blood samples were collected for the estimation of hyperthyroidism in nephropathy patients. Thyroid stimulating hormone (TSH), thyroxin, and triiodothyronine were estimated using the chemilumeniscent techniques. Serum creatinine levels were estimated through the modified kinetic phenomenon (Jaffe's reaction). Serum urea levels were estimated through the urease method and uric acid levels were recorded. The mean age of hypothyroid patients was 37.38 years. It was 34.13 years for patients with the hyperthyroid state, while for the normal patients it was 35.46 years. Women comprised 70% of the hypothyroid patients, whereas among the normal patients their percentage was 29%. Serum TSH level $(7.11 \pm 0.001 \text{ mIU/L})$ was significantly higher in hypothyroid patients, although it decreased in hyperthyroid patients (0.22 ± 0.001) as compared to the corresponding values in healthy patients (2.54 ± 0.001) . The values of T3 $(52.3 \pm 0.05 \text{ ng/dl})$ and T4 (2.217 ± 0.001) decreased slightly in hypothyroid patients as compared to the healthy patients (104 \pm 0.001 and 6.667 \pm 0.001 respectively), although they remained statistically significant. T3 (356.12 \pm 0.001) and T4 (17.99 \pm 0.001) significantly increased in hyperthyroid patients. The correlation between thyroid dysfunction and nephropathy was found to be significant. Gender and age proved to be the most important factors for these pathological conditions. Renal function biomarkers including GFR, serum creatinine, urea and uric acid were found to have an association with changes in the thyroid hormones.

Keywords: hyperthyroidism, hypothyroidism, nephropathy, triidothyroxine, thyroid profile

1. Introduction

The thyroid gland produces two hormones: thvroxin (T4) and triiodothyronine (T3). These hormones are regulated through the anterior pituitary hormone, the thyroid stimulating hormone (TSH) which is under the control of the hypothalamic chemical messengers, and the thyrotropin hormone (TRH) [1]. The thyroid gland produces almost 100μ g thyroxin and 30μ g triiodothyronine on a daily basis, of which 20% is produced by the thyroid gland and the remaining 80% is produced through the de-iodination of T4 [2]. Thyroid hormones are typically intended for neural separation and metabolic control and they also play a role in cell differentiation during development [3]. Thyroid disorders are quite common and occur due to



endocrine dysfunction. Hypothyroidism occurs because of the underactivity of the thyroid gland. This disorder is indicated if the TSH level is high along with decreased T3 and T4 levels [4].

Thyroid hormone affects both the kidney morphology and its functions. Kidneys involved in metabolism are and elimination of the thyroid hormones. Thyroid's improper effect on the renal function leads to change in the blood flow, the glomerular filtration rate and metabolic products such as creatinine. urea and uric acid [5]. Due to the structural and functional changes that interfere in the production of the adequate levels of the thyroid hormones, hypothyroid and hyperthyroid states occur [6]. In hyperthyroidism, both renal blood flow (RBF) and the glomerular filtration rate (GFR) increase as compared to the hypothyroid state in which RBF decreases along with the glomerular filtration rate [7,8]. Creatinine is directly associated with TSH, although it has an inverse effect on both T3 and T4 profiles. It increases in the hypothyroid state due to the lower level of GFR, which in turn decreases the renal clearance and alteration, the ability of water excretion and vice versa [9]. Thyroid disorders are also directly linked with urea. TSH stimulates the production of protein synthesis. As protein production increases, the metabolism also increases which results in urea production [10]. Uric acid is the end product of purine metabolism. Uric acid is directly related with TSH, although it has an inverse effect on T3 and T4. It increases in the hypothyroid state which may be a result of either myopathy associated with hypothyroidism or improper renal clearance due to the decreased GFR [11], myopathy patients since show а decreased renal urate excretion rate as

compared to the hyperthyroid patients $[\underline{12}]$.

The current study evaluates the correlation between the thyroid profile and the renal profile in order to indicate whether nephropathy in patients occurs either due to hypothyroidism or hyperthyroidism.

2. Methodology

The current study was conducted on 100 nephropathy patients of which 57 were female patients and 43 were male patients. The diagnosis was based on low serum T3 and T4 levels associated with a high level of TSH in nephropathy patients along with a high level of serum creatinine. For this study, nephropathy patients with a low level of serum creatinine were excluded. Written consent from all the patients was taken after explaining to them that their personal information would not be disclosed at any cost and the data would only be used for research purposes. No grant was received for this research work from any funding agency working in the public, commercial, or not-for-profit sectors.

Venous blood samples were collected for the estimation of hypothyroidism or hyperthyroidism in nephropathy patients. For hypo and hyperthyroidism, the diagnostic criteria were the estimation of the serum TSH levels along with T3 and T4. For nephropathy, the diagnostic criteria were serum creatinine, urea and uric acid estimation.

2.1. Thyroid Profile

TSH, thyroxin, and triiodothyronine were estimated using chemilumeniscent techniques on Architect-C4000 fully automated analyzer.



2.2. Renal Function Tests

Serum creatinine levels were estimated using the modified kinetic phenomenon (Jaffe's reaction) [13]. Serum urea levels were estimated through the urease method [14] and uric acid levels were recorded using the modified Trinder peroxidase method [15]. The mean age of patients was calculated to be 36 years. The chemistry analyzer used for RFT estimation operates on the photometric technique.

2.3. Equation for GFR Estimation

The MDRD formula is given below.

GFR $(ml/min/1.73m^2) = 186 x$ (Creatinine/88.4)^{-1.154} x (Age)^{-0.203} x (0.742 if female)

2.4. Statistical Analysis

Data was entered using Microsoft Excel 2007. Demographic data analysis was performed using SPSS. Pearson correlation was used to test whether TSH, T3 and T4 correlated with serum creatinine, urea and uric acid. *P*-value <0.05 was considered statistically significant.

3. Results

The study was conducted among associated type of patients to determine the scientific relationship between nephropathy and thyroidism. The mean age of hypothyroid patients was 37.38 vears. It was 34.13 years for patients with the hyperthyroid state and for the normal patients it was 35.46 years. Women comprised 70% of the hypothyroid patients, whereas among the normal patients their percentage was 29%, as shown in Table 1.

Serum TSH level (7.11 \pm 0.001 mIU/L) significantly increased in hypothyroid patients but decreased in hyperthyroid patients (0.22 \pm 0.001) as compared to the corresponding values in the healthy patients (2.54 \pm 0.001). The values of T3 (52.3 \pm 0.05 ng/dl) and T4 (2.217 \pm 0.001) decreased slightly in hypothyroid patients as compared to the healthy patients (104 \pm 0.001 and 6.667 \pm 0.001, respectively), although they remained statistically significant. The values of T3 (356.12 \pm 0.001) and T4 (17.99 \pm 0.001) significantly increased in hyperthyroid patients, as shown in Table 2.

Table 1. Age and Sex Distribution in Thyroid Cases and Healthy Control Cases				
Variables	5	Hypothyroid	Hyperthyroid	Normal / Control
Age		37.38 ± 12.8	34.31 ± 12.3	35.46 ± 11.5
Gender	Male	13	30	40
	Female	40	17	60

Table 1. Age and Sex Distribution in Thyroid Cases and Healthy Control Cases

Table 2. Comparison between Serum TSH, T3 and T4 Values Obtained in
Hypothyroid and Healthy Controls

Parameters	Hypothyroid	Hyperthyroid	Normal
TSH (mIU/L)	7.11 ± 0.001	0.22 ± 0.001	2.54 ± 0.001
T3 (ng/dl)	52.3 ± 0.001	356.12 ± 0.001	104 ± 0.001
T4 (mg/dl)	2.217 ± 0.001	17.99 ± 0.001	6.667 ± 0.001



The mean serum level of urea was significantly higher in the hypothyroid state as compared to the healthy subjects (39.07 mg/dl vs 15.80 mg/dl), although it was statistically low in hyperthyroid patients (2.81 mg/dl) with the p-value <0.001. Patients with the hypothyroid state had a statistically significant high level of uric acid as compared to the healthy subjects (9.252 mg/dl vs 4.445 mg/dl), although hyperthyroid patients had a statistically significant low value (1.46 mg/dl) with the p-value 0.0005. The serum creatinine level was significantly higher in hypothyroid patients due to the low level of GFR in these patients as compared to the normal subjects (4.141 mg/dl vs 2.100 mg/dl), although hyperthyroid patients have a low value (1.12 mg/dl) with the p-value 0.000, as shown in Table 3.

When hypothyroidism and nephropathy were compared, TSH, T3 and T4 values

showed significant changes in the thyroid function. On the other hand, the parameters of the renal profile including serum creatinine, urea and uric acid, also showed a significant association. Age group and gender have an insignificant association with both the thyroid and renal profiles as shown in Table 4.

Glomerular filtration rate is considered as an important function of the kidneys in both normal and nephropathy patients. In the hypothyroid state, GFR had a low $ml/min/1.73m^{2}$) value (17.55 compared to the healthy controls (59.65 ml/min/1.73m^{2}). In the hyperthyroid state. GFR had a statistically high value (71.07 ml/min/1.73m²). GFR showed a statistically significant association with the parameters of the thyroid profile (TSH, T3 and T4) and the thyroid conditions of the subjects with *p*-value 0.001.

Hyperthyroid Parameters Hypothyroid Normal $4.141 \pm < 0.001$ $1.12 \pm < 0.001$ $2.100 \pm < 0.001$ Serum Creatinine (mg/dl)Urea (mg/dl) $39.07 \pm < 0.001$ $2.81 \pm < 0.001$ $15.82 \pm < 0.001$ Uric Acid (mg/dl) 9.252 ± 0.0005 1.46 ± 0.0005 4.455 ± 0.0005

Table 3. Biochemical Parameters of RFTs in Hypothyroid and Healthy Controls

Table 4. Comparison	of the	Thyroid	Profile	and	the	Renal	Profile	Based	on	Age
Group and Gender										

Parameters	Age (p-value)	Gender (p-value)
TSH (mIU/L)	0.675	0.396
T3 (ng/dl)	0.832	0.697
T4 (mg/dl)	0.832	0.694
Serum Creatinine (mg/dl)	0.478	0.196
Urea (mg/dl)	0.796	0.296
Uric Acid (mg/dl)	0.933	0.697

(p=Pearson correlation)

4. Discussion

Endocrine's normal functioning is essential for the proper functioning of the body and normal homeostasis. Any endocrine dysfunction may lead to severe health conditions. Thyroid is one of the most vital endocrine glands and has an obvious influence on protein synthesis, cellular growth, water and electrolvte balance and renal development [16]. Thyroid hormones may cause interference with the renal blood flow due to their association with cardiovascular alterations [17. 18]. Hypothyroidism is often associated with severe alterations in the blood lipid profile, greater risk of atherosclerosis and endothelial damage [19, 20, 21]. The interplay between thyroidism and nephropathy is very common and wellrecognized [22, 23, 24].

Iodine deficiency is considered as the key factor behind the disturbed thyroid hormones [25] which ultimately disrupt the renal profile, while age, gender, smoking. genetic predisposition, ethnicity, alcoholism, drug exposure and auto-immune diseases have also been observed have significant to а association with the prevalence of the thyroid disease [26, 27, 28]. In the current study, thyroid disorder was observed to be more prevalent in females (57%) than males (43%) which may be due to the problems occurring during hormonal unrest including prolonged periods or physical and mental stress in females. In the current investigation, 40% and 17% of female patients were found be suffering from to hypothyroidism and hyperthyroidism, respectively. The hypothyroid state is likely more common in females than males due to the property of estrogen to increase the response of TSH towards thyrotropin releasing hormone (TRH) [29]. Similar results have been reported by various researchers [$\underline{30}$, $\underline{31}$, $\underline{32}$, $\underline{33}$]. Age was observed to be associated significantly with the thyroid and renal profiles (Table 4). There are several studies which report thyroid dysfunction with age [$\underline{34}$, $\underline{35}$, $\underline{36}$]. A study conducted by Bensenor et al. [$\underline{37}$] concluded that the disruption of thyroid profile has an association with the age of the patient.

In this study, it was shown that nephropathy has a positive correlation with the pathological conditions of the thyroid hormones. Moreover, TSH was observed to have an inverse relation with T3 and T4 in both hypo and hyper states of the thyroid patients (Table 2). TSH was significantly higher in level hypothyroid patients but much lower in hyperthyroid patients as compared to the control group. Whereas, T3 and T4 serum levels were lower in hypothyroid patients but higher in hyperthyroid patients. A similar pattern of association between TSH, T3 and T4 in thyroidism affected patients was reported by Jia et al. [38].

Biochemical parameters of nephropathy (serum creatinine, urea and uric acid) were found to be inversely related with T3 and T4 but directly related with TSH (Table 2-3). Nephropathy parameters were elevated in hypothyroidism but declined in hyperthyroid patients as compared to the control group. Therefore, hypothyroidism is considered as an independent risk factor for nephropathy [39]. Several studies have revealed the altered pattern of the thyroid profile in association with nephropathy. A study conducted by Suher et al. revealed a significant increase in the nephropathy parameters in hypothyroid patients [40]. Mehta et al. evaluated the thyroid profile in renal failure patients and concluded that a decrease in thyroid



hormones was directly linked with an increase in renal damage $[\underline{41}]$.

The renal parameters are strongly influenced by the pathological conditions of thyroid dysfunction. In the current study, patients with both hypothyroidism and hyperthyroidism showed significant changes in their renal function. Dysfunction in the thyroid hormone profile influences several renal functions including RBF, sodium (Na⁺) and calcium (Ca⁺²) reabsorption and angiotensinase activity [42, 43]. These changes are either expressed as serum creatinine or GFR. Serum creatinine significantly raised level was in hypothyroid patients with *p*-value <0.001. It was elevated in hypothyroid patients due to a reduction in GFR and RBF because of certain hemodynamic changes [44]. There are several previous studies that reported an increased creatinine level with a decreased GFR [45, 46]. Rajagopalan et al. reported a negative correlation of the thyroid hormones with urea and creatinine [47].

A statistically significant rise in the uric acid level was observed in hypothyroid patients with *p*-value <0.001. Urea is the product of protein breakdown which was found to be significant in the hypothyroid state patients. of Hyperuricemia is associated with endocrine disorders. In other studies, it hyperuricemia was observed that occurred due to an increased production of uric acid in myopathy associated with hypothyroidism or due to a reduction in the renal uric acid clearance associated with hypothyroidism [48].

5. Conclusion

The correlation between thyroid dysfunction and nephropathy was found to be significant. Gender and age proved to be the most important factors for these pathological conditions. Female patients and older patients are at a greater risk of thyroid hormones' alterations leading to nephropathy. Renal function biomarkers including GFR, serum creatinine, urea and uric acid were found to have an association with thyroid hormones' alterations.

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