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Thyroid Dysfunction and Kidney Dysfunction

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ABSTRACT

Objectives: The incidence and prevalence of chronic kidney disease (CKD) are rising worldwide. It is becoming more common in the developing world with the increasing impact of non-communicable diseases in these countries. Also, autoimmune disorders, including thyroid dysfunction are more common and may worsen the clinical status of patients with CKD. We sought to determine the thyroid status in patients with CKD and explore the clinical, biochemical, immunological, and hematological parameters that can be affected by thyroid dysfunction among CKD patients. ***Methods***: We conducted a cross-sectional observational study at the Royal Hospital, Muscat. The data was progressively collected for all newly diagnosed CKD patients with no known history of thyroid disease from January 2018 to December 2019. Assessment of thyroid status was performed at their initial diagnosis. ***Results:*** During the study period, 121 females (40.3%) and 179 males (59.7%) were diagnosed with CKD with no prior thyroid diseases. The mean age for females and males were 53.6±16.5 and 49.5±16.5 years, respectively. There were 35 patients with thyroid dysfunction with a prevalence of 11.7%. Of these, 22 patients (62.9%) had subclinical hypothyroidism, and 13 (37.1%) had subclinical hyperthyroidism. Total cholesterol and low-density lipoprotein were higher in hypothyroid patients. Urea was higher in hyperthyroid patients with CKD, and hemoglobin level was significantly lower. ***Conclusions:*** Thyroid dysfunction was not uncommon among CKD patients, with subclinical hypothyroidism more common than subclinical hyperthyroidism. Thyroid dysfunctions coexisted with kidney dysfunction. These hormonal axis dysfunctions may not be apparent at first presentation; and therefore, may require close clinical and laboratory evaluations.

Researchers have investigated the interactions between kidney function and thyroid hormonal status for years. For example, the hormonal activity of the thyroid gland influences the prenatal kidney and post-natal growth and function. Also, the metabolism and elimination of thyroid hormone are controlled by maintaining good kidney function.[1,2] In addition to the alteration of the hypothalamic-pituitary-thyroid hormone, Lim et al,[2,3] reported that end-stage kidney disease (ESKD) alters the peripheral thyroid hormone metabolism.

The body water and various electrolyte equilibrium in different body compartments are influenced by the thyroid hormonal balance. The kidney is an important end-organ target for thyroid hormonal action and plays a role in the control of metabolic rate and abolition of thyroid hormones.[4] The decrease in the action of thyroid hormones is escorted by an incapability to get rid of an oral fluid overload. This effect is not due to incomplete suppression of vasopressin production or a decrease in the re-absorptive capacity in the tubule-dilutor segment of the kidney but rather to a drop in the glomerular filtration rate (GFR).[1]

Among patients with chronic kidney disease (CKD), the identification of hypothyroidism can be easily missed, because of the overlap in the symptoms of CKD and hypothyroidism.[5] Well-timed diagnosis and management of hypothyroidism may avoid deterioration of patient condition and extend survival.

Several factors may lead to thyroid abnormalities among CKD patients. The circulating and tissue -active forms of triiodothyronine (T3) were found to be low secondary to the deiodinase activity diminution.[2,3] Because of diminished kidney secretion, inorganic iodide generated by residual deiodinase activity accumulates in stages 4 and 5 of CKD, which dampens hormonal synthesis in the

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thyroid gland.[6] On the other hand, among CKD patients, the accumulation of uremic poisonous solutes changes the vital (hypothalamic) control of the pituitary gland, and the thyroid-stimulating hormone (TSH) response to thyrotropin-releasing hormone is abnormally low.[2,3] However, the feedback loop mechanism of the thyroid–pituitary remains intact because steady-state plasma TSH remains substantially normal and TSH undergoes the expected rise after thyroidectomy. Also, the toxic uremia poisonous solutes inhibit the capability of protein binding of thyroxin.[7] Furthermore, researchers in the last decade found that inflammation and systemic metabolic acidosis produced by patients with CKD might alter the various thyroid function.[8–10]

The kidney also contributes to the metabolism and clearance of the iodine primarily through GFR alterations. Among patients with CKD, serum iodine concentrations are elevated. However, this high level is not parallel to the degree of deterioration of GFR and CKD stages.[5,7] The Wolff–Chaikoff effect is an auto-monitoring trend of the creation of hormones of the thyroid inside its follicles, and the discharge of its hormones to the circulation is hindered by the high iodine level in the blood. Among CKD, the high prevalence of thyroid abnormalities, such as goiter and hypothyroidism, has been suggested to be due to excess iodine levels.[2,3,5]

A few researchers found that limiting the amount of iodine in food can abolish the development of hypothyroidism and hence avoid the requirement for replacement therapy with thyroxine among patients with CKD on hemodialysis.[11,12] Researchers found that in patients with subclinical hypothyroidism in CKD, thyroxine supplementation may reduce the progression of CKD towards ESKD; and hence improve GFR.[13]

We have > 2500 patients on hemodialysis therapy and 250 patients on peritoneal dialysis. In addition, it was reported that 1% of the population aged 40 years and over have severe kidney disease, 9% have moderate kidney disease, and 29% have mild kidney disease.[14–16] Hence, there is a need to assess the presence of thyroid dysfunction and its relation to kidney function at the first encounter of diagnosis with kidney dysfunction. This study evaluated the thyroid function tests and various clinical and laboratory findings among patients with CKD at the initial clinical encounter.

METHODS

The study was approved by the Scientific Research Committee at the Royal Hospital, Muscat, Oman, Ministry of Health (MOH/CSR/18/9073). The study was performed according to the 1964 Declaration of Helsinki and its later amendments. Each participant freely gave informed consent to undergo biopsy and laboratory investigations. This cross-sectional observational clinical study was conducted at the Royal Hospital. It has an excellent medical record and IT system where everything is computerized and has received a well-recognized international certificate of excellence for its achievement in its electronic medical file system called Al Shifa. The hospital includes central laboratory that tests all hormone studies, including thyroid hormones, for all patients all over the country. All data, including clinical, laboratory, and radiological data were collected prospectively in the Al Shifa. We recruited 300 newly diagnosed CKD patients with no history of thyroid disease who attended the adult nephrology outpatient clinic from 2018 to 2019 for assessment of thyroid status.

The following data were collected: age (years), body weight (kg), height (cm), body mass index (BMI) (kg/m^2), diabetes mellitus, hypertension, TSH, thyroxine (free T4), serum creatinine, blood urea, e-GFR (mL/min/m^2), serum albumin, hemoglobin (Hb) level, white blood cell (WBC) count, plasma glucose level, hemoglobin A_{1c} (HbA_{1c}), total cholesterol (TC), low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglyceride (TG), urinary protein/creatinine ratio, red blood cells in the urine, complement level of C3 and C4, antinuclear antibody (ANA), anti-neutrophil cytoplasmic antibodies (ANCA), immunoglobulin (Ig) A level, virology screen, bone profile, parathyroid hormone (PTH), and dual-energy X-ray absorptiometry (DEXA) study. Hypothyroidism is defined as TSH being higher than the normal range and low free T4. Subclinical hypothyroidism when TSH is high, but free T4 is still within normal values range.

We performed immunoassay on the Siemens Atellica System, Germany. Both TSH and T4 were concurrently measured in the same laboratory. Hyperthyroidism was defined as low TSH and high free T4. Subclinical hyperthyroidism was defined as a low TSH but normal free T4. The normal range for TSH was 0.2–4.5 mIU/L and 8–24 pmol/L for free T4.

Table 1: Clinical parameters of the 300 chronic kidney disease patients.

Parameters	Male, mean ± SD	Female, mean ± SD	95% CI	*p*-value
Age, years	49.5 ± 16.5	53.6 ± 16.5	49.31 – 53.13	0.038
Body mass index, kg/m^2	28.7 ± 7.4	27.5 ± 7.9	26.97 – 29.37	0.336
	Male, n	**Female, n**	**Total, %**	***p*-value**
Hypertension	116	93	209 (69.7)	0.036
Diabetes mellitus	88	59	147 (49.0)	0.871
Thyroid dysfunction	13	22	35 (11.7)	0.004

Table 2: Biochemical and hematological parameters of the 300 chronic kidney disease patients.

Parameters	Male, mean ± SD	Female, mean ± SD	95% CI	*p*-value
TSH, miu/L	2.3 ± 7.4	2.2 ± 3.3	1.63–3.03	0.882
T4, pmol/L	12.4 ± 3.7	13.8 ± 4.1	12.01–14.51	0.270
Urea, mmol/L	13.9 ± 9.9	15.1 ± 11.0	13.22–15.58	0.311
Creatinine, umol/L	321.6 ± 323.5	300.0 ± 235.7	279.83–345.98	0.530
GFR, mL/min/1.73 m^2	41.8 ± 28.4	32.2 ± 26.1	34.80–41.13	0.003
Urine PCR, mg/mmoL	312.9 ± 601.9	466.3 ± 581.3	299.66–445.90	0.043
Hematuria RBC/HPF	47.8 ± 79.2	118.1 ± 541.4	30.96–116.70	0.119
Albumin, g/L	35.4 ± 6.2	32.6 ± 6.2	33.57–35.02	< 0.001
ALP, iu/L	108.5 ± 89.7	132.5 ± 191.4	102.32–137.17	0.147
Calcium, mmol/L	2.3 ± 0.1	2.3 ± 0.2	2.36–2.40	0.349
Phosphate, mmol/L	2.1 ± 7.7	1.3 ± 0.4	1.16–2.53	0.266
PTH, pmol/L	22.0 ± 6.0	27.5 ± 34.9	20.6–28.12	0.150
Hemoglobin, g/dL	12.4 ± 2.5	10.8 ± 2.0	11.50–12.07	< 0.001
WBC, × 10^9/L	7.1 ± 2.4	7.46 ± 3.2	6.94–7.58	0.318
Platelets, × 10^9/L	259.1 ± 78.7	275.4 ± 109.3	255.21–276.23	0.133
HbA_{1c}, %	6.60 ± 1.8	6.3 ± 1.6	6.25–6.77	0.411
Glucose, mmol/L	7.19 ± 3.4	6.7 ± 3.1	6.61–7.41	0.285
TC, mmol/L	4.8 ± 1.2	5.0 ± 1.4	4.76–5.09	0.147
LDL, mmol/L	3.0 ± 1.0	3.10 ± 1.1	2.92–3.19	0.629
HDL, mmol/L	1.1 ± 0.7	1.2 ± 0.4	1.12–1.27	0.048
TG, mmol/L	1.6 ± 1.0	1.89 ± 3.1	1.27–2.51	0.460
IgA, umol/L	2.8 ± 2.1	2.9 ± 2.4	2.48–3.26	0.801

THS: thyroid-stimulating hormone; T4: thyroxine; GFR: glomerular filtration rate; PCR: polymerase chain reaction; ALP: alkaline phosphatase; PTH: parathyroid hormone; WBC: white blood cell; HbA_{1c}: hemoglobin A1c; TC: total count; LDL: low-density lipoprotein; HDL: high-density lipoprotein; TG: thyroglobulin; Ig: immunoglobulin.

Data were presented as numbers and percentages. Continuous data were presented as mean ± SD. Student *t*-test was used to compare the means of the two groups. One-way analysis of variance test was performed to compare parameters between groups. The relationship between parameters was evaluated by Pearson correlation analysis. A *p*-value of < 0.050 was considered statistically significant. All patients were classified by sex and then those with normal thyroid function and thyroid dysfunction. All statistical analyses were carried out using STATA software.

RESULTS

We identified 300 newly diagnosed CKD patients at their initial visit to the outpatient department clinics [Table 1]. The mean age for females was 53.6±16.5 years, and for male was 49.5±16.5 years ($p = 0.038$). The mean BMI was 27.5±7.9 kg/m^2 and 28.7±7.4 kg/m^2 for females and males, respectively ($p = 0.336$). Hypertension was present in 69.7% and diabetes in 49.0% of patients. Among females, diabetes was present in 40.1% and hypertension in 93 patients. Among males, hypertension was present in 88 patients and diabetes in 116

Table 3: Immunological/virology parameters of the 300 chronic kidney disease patients.

Parameters	Male, n	Female, n	*p*-value
ANA (Positive)	9	10	0.450
ANCA (Positive)	1	3	0.130
C3 (low)	8	11	0.111
C4 (low)	1	7	0.006
Virology status			
HBV (Positive)	12	5	0.650
HCV (Positive)	5	4	0.809
HIV (Positive)	0	0	

ANA: antinuclear antibodies; ANCA: antineutrophil cytoplasmic antibodies; C3: component 3; C4: component 4; HBV: hepatitis B virus; HCV: hepatitis C virus; HIV: human immunodeficiency virus.

Table 4: Radiological parameters; DEXA scan and abdomen US of the 300 chronic kidney disease patients.

Parameters	Male, n	Female, n	Total, %
DEXA			
Normal	56	61	117 (39.0)
Osteopenia	69	57	126 (42.0)
Osteoporosis	31	26	57 (19.0)
Total	156	144	300 (100)
p-value			0.863
Ultrasound			
Normal US	87	88	175
Abnormal US	35	90	125
Total	122	178	300
p-value			0.001

DEXA: dual X-ray absorptiometry; US: ultrasound.

patients. The prevalence of thyroid dysfunction was 11.7% and was more prevalent in females than males ($p = 0.004$).

Table 2 showed the comparison of biochemical parameters of males and females. The e-GFR level was significantly lower in females ($p = 0.003$) although the creatinine level showed no statistical difference. Moreover, the urine protein creatinine ratio (PCR) was higher in females than in males ($p = 0.043$). In addition, the albumin and HDL levels were both significantly lower in the female group.

Table 5: Mean biochemical and hematological parameters of the 300 chronic kidney disease patients by their thyroid status.

Parameters	Normal thyroid	Thyroid dysfunction	95% CI	*p*-value
TSH, miu/L	1.6 ± 0.8	7.6 ± 17.0	1.63–3.03	< 0.001
T4, pmol/L	13.0 ± 3.3	13.4 ± 4.4	12.01–15.26	0.780
Creatinine, umol/L	311.6 ± 299.2	322.7 ± 233.6	279.83–345.98	0.831
GFR, mL/min/1.73 m^2	39.1 ± 28.1	29.2 ± 23.7	34.79–41.12	0.047
Urea, mmol/L	13.9 ± 9.2	17.9 ± 16.3	13.22–15.58	0.032
Urine PCR, mg/mmoL	350.6 ± 583.2	555.1 ± 689.4	299.66–445.90	0.087
Hematuria, RBC/HPF	74.7 ± 35.2	67.0 ± 89.1	30.96–116.70	0.913
Albumin, g/L	34.61 ± 6.1	31.9 ± 7.5	33.57–35.02	0.018
ALP, iu/L	117.8 ± 145.6	121.0 ± 90.2	102.32–134.17	0.898
Calcium, mmol/L	2.3 ± 0.1	2.3 ± 0.1	2.36–2.40	0.773
Phosphate, mmol/L	1.9 ± 6.3	1.3 ± 0.2	1.16–2.53	0.615
PTH, pmol/L	25.2 ± 31.1	18.1 ± 21.7	20.60–28.12	0.220
Hemoglobin, g/dL	11.9 ± 2.4	10.5 ± 2.2	11.50–12.07	0.004
WBC, × 10^9/L	7.1 ± 2.6	8.3 ± 3.5	6.94–7.58	0.019
Platelets, × 10^9/L	265.2 ± 92.5	269.1 ± 93.5	255.21–276.23	0.816
HbA_{1c}, %	6.4 ± 1.7	6.9 ± 1.9	6.25–6.77	0.231
Glucose, mmol/L	6.9 ± 3.3	7.1 ± 3.1	6.61–7.41	0.811
TC, mmol/L	4.8 ± 1.3	5.2 ± 1.5	4.76–5.09	0.104
LDL, mmol/L	3.0 ± 1.0	3.4 ± 1.3	2.92–3.19	0.031
HDL, mmol/L	1.1 ± 0.6	1.2 ± 0.4	1.12–1.27	0.855
TG, mmol/L	1.7 ± 2.2	1.6 ± 1.0	1.51–2.03	0.715
IgA, umol/L	2.8 ± 2.3	2.9 ± 2.0	2.48–3.26	0.855

THS: thyroid-stimulating hormone; T4: thyroxine; GFR: glomerular filtration rate; PCR: polymerase chain reaction; RBC: red blood cell; HPF: high power field; ALP: alkaline phosphatase; PTH: parathyroid hormone; WBC: white blood cell; HbA_{1c}: hemoglobin A1c; TC: total count; LDL: low-density lipoprotein; HDL: high-density lipoprotein; TG: thyroglobulin; Ig: immunoglobulin.

However, other biochemical parameters like TSH, T4, TC, LDL, TG, calcium, phosphate, alkaline phosphatase (ALP), PTH, urea, and creatinine did not show any statistical difference between male and female groups.

Hb was significantly lower in females. However, platelets and WBC levels showed no statistical difference.

It showed that low levels of complement C4 were significantly more frequent in females than males [Table 3]. Also, the virology status, specifically hepatitis B, hepatitis C, and HIV showed no significant difference.

Table 4 shows radiological investigations. DEXA scan was done, and 39.0% showed normal results, 42.0% showed osteopenia, and 19.0% had osteoporosis. The abdomen ultrasound (US) results revealed more CKD changes in females than males.

There were 35 patients with thyroid dysfunction with a prevalence of 11.7%. In those with thyroid dysfunction, 22 patients (62.9%) had subclinical hypothyroidism, and 13 (37.1%) had subclinical hyperthyroidism. The thyroid dysfunction group had a higher mean age of 56.8±17.8 years compared to 50.4±16.5 years than those who had normal thyroid function with a *p*-value of 0.030. BMI, diabetes mellitus, and hypertension status were similar in both groups.

Urea was significantly higher in the thyroid dysfunction group and GFR was significantly lower in this group [Table 5]. Both albumin and Hb were significantly lower in the thyroid dysfunction group. WBCs and LDL were both higher in the thyroid dysfunction group. Other biochemical, hematological, and immunological parameters, and virology status did not show any statically significant difference between the normal thyroid patients and those with thyroid dysfunction.

Biochemical parameters showed that TSH was significantly higher in the hypothyroid group and free T4 was significantly lower [Table 6]. Kidney parameters including serum creatinine, GFR, urea,

Table 6: Mean biochemical and hematological parameters of the 300 chronic kidney disease patients by their thyroid status.

Parameters	Normal thyroid	Hypothyroid	95% CI	*p*-value
TSH, miu/L	1.6 ± 0.8	12.1 ± 20.3	1.71–3.16	< 0.001
T4, pmol/L	13.0 ± 3.3	10.8 ± 2.2	10.94–13.18	0.044
Creatinine, umol/L	311.6 ± 299.2	286.2 ± 210.2	275.60–343.72	0.679
GFR, mL/min/1.73 m^2	39.1 ± 28.1	34.0 ± 26.3	35.46–41.98	0.411
Urea, mmol/L	13.9 ± 9.2	14.5 ± 10.7	12.89–15.07	0.769
Urine PCR, mg/mmoL	350.6 ± 583.2	570.4 ± 726.5	203.07–441.67	0.122
Hematuria, RBC/HPF	74.7 ± 35.2	59.1 ± 85.3	28.84–118.23	0.857
Albumin, g/L	34.6 ± 6.1	31.8 ± 8.5	33.66–35.14	0.051
ALP, iu/L	117.8 ± 145.6	125.8 ± 109.5	101.86–135.09	0.802
Calcium, mmol/L	2.3 ± 0.1	2.3 ± 0.1	2.36–2.40	0.946
Phosphate, mmol/L	1.9 ± 6.3	1.3 ± 0.2	1.15–2.58	0.664
PTH, pmol/L	25.2 ± 31.1	16.0 ± 12.2	20.63–28.31	0.189
Hemoglobin, g/dL	11.9 ± 2.4	11.2 ± 2.3	11.60–12.18	0.215
WBC, × 10^9/L	7.1 ± 2.6	8.5 ± 4.1	6.90–7.56	0.021
Platelets, × 10^9/L	265.2 ± 92.5	271.1 ± 84.5	255.05–276.39	0.772
HbA_{1c}, %	6.4 ± 1.7	7.2 ± 2.2	6.59–7.42	0.855
Glucose, mmol/L	6.9 ± 3.3	7.1 ± 3.7	6.59–7.41	0.811
TC, mmol/L	4.8 ± 1.2	5.5 ± 1.6	4.77–5.10	0.033
LDL, mmol/L	3.0 ± 1.0	3.6 ± 1.4	2.91–3.19	0.011
HDL, mmol/L	1.1 ± 0.6	1.3 ± 0.4	1.12–1.28	0.438
TG, mmol/L	1.7 ± 2.2	1.7 ± 1.2	1.51–2.06	0.852
IgA, umol/L	2.8 ± 2.3	3.2 ± 2.4	2.48–3.26	0.611

THS: thyroid-stimulating hormone; T4: thyroxine; GFR: glomerular filtration rate; PCR: polymerase chain reaction; RBC: red blood cell; HPF: high power field; ALP: alkaline phosphatase; PTH: parathyroid hormone; WBC: white blood cell; HbA_{1c}: hemoglobin A1c; TC: total count; LDL: low-density lipoprotein; HDL: high-density lipoprotein; TG: thyroglobulin; Ig: immunoglobulin.

Table 7: Mean biochemical and hematological parameters of 300 chronic kidney disease patients by their thyroid status.

Parameters	Normal thyroid	Hyperthyroid	95% CI	*p*-value
TSH, miu/L	1.6 ± 0.8	0.1 ± 0. 1	1.45–1.66	< 0.001
T4, pmol/L	13.0 ± 3.3	16.6 ± 4.5	12.84–16.09	0.023
Creatinine, umol/L	311.6 ± 299.2	348.6 ± 240.3	279.98–350.05	0.387
GFR, mL/min/1.73 m^2	39.1 ± 28.1	21.0 ± 16.5	34.97–41.58	0.023
Urea, mmol/L	13.9 ± 9.2	23.6 ± 22.	13.16–15.61	< 0.001
Urine PCR, mg/mmoL	350.6 ± 583.2	523.0 ± 644.1	282.73–219.51	0.387
Hematuria (RBC/HPF)	74.7 ± 35.2	80.5 ± 98.5	28.87–121.05	0.959
Albumin, g/L	34.6 ± 6.1	32.0 ± 6.4	33.76–35.22	0.136
ALP, iu/L	117.8 ± 145.6	113.0 ± 44.2	100.82–134.46	0.905
Calcium, mmol/L	2.38 ± 0.1	2.3 ± 0.1	2.36–2.40	0.563
Phosphate, mmol/L	1.9 ± 6.3	1.4 ± 0.3	1.15–2.62	0.794
PTH, pmol/L	25.0 ± 31.1	21.9 ± 33.3	21.04–29.14	0.736
Hemoglobin, g/Dl	11.94 ± 2.5	9.6 ± 1.6	11.53–12.13	0.001
WBC, × 10^9/L	7.1 ± 2.6	7.8 ± 2.3	6.84–9.28	0.333
Platelets, × 10^9/L	265.2 ± 92.5	265.6 ± 110.8	254.28–276.30	0.987
HbA_{1c}, %	6.4 ± 1.7	6.3 ± 1.1	6.18–6.71	0.884
Glucose, mmol/L	6.9 ± 3.3	7.1 ± 1.9	6.59–7.41	0.869
TC, mmol/L	4.8 ± 1.2	4.8 ± 1.1	4.71–5.04	0.842
LDL, mmol/L	3.0 ± 1.0	3.0 ± 0.8	2.87–3.14	0.809
HDL, mmol/L	1.1 ± 0.6	1.0 ± 0.2	1.10–1.27	0.400
TG, mmol/L	1.7 ± 2.2	1.5 ± 0.5	1.49–2.06	0.704
IgA, µmol/L	2.8 ± 2.3	2.4 ± 1.3	2.44–3.24	0.720

THS: thyroid-stimulating hormone; T4: thyroxine; GFR: glomerular filtration rate; PCR: polymerase chain reaction; RBC: red blood cell; HPF: high power field; ALP: alkaline phosphatase; PTH: parathyroid hormone; WBC: white blood cell; HbA_{1c}: hemoglobin A1c; TC: total count; LDL: low-density lipoprotein; HDL: high-density lipoprotein; TG: thyroglobulin; Ig: immunoglobulin.

hematuria, and proteinuria were similar in both hypothyroid and normal thyroid groups. WBC, TC, and LDL were higher in hypothyroid patients compared with normal thyroid patients.

Other parameters, including immunological, virology status, CKD findings in the abdominal US and osteoporosis in DEXA scan did not show any significant difference between hypothyroid and normal thyroid groups.

TSH was significantly lower in the hyperthyroid group with a mean of 0.1 miu/L and free T4 was significantly higher with a mean of 16.6 pmol/L [Table 7]. GFR was significantly lower in the hyperthyroid group. However, creatinine was not showing any statistical difference between the two groups. Also, urea levels were higher in the hyperthyroid group than in the normal thyroid group with a mean of 23.6 mmol/L ($p < 0.001$). Other parameters like hematuria and proteinuria were similar between the groups. Moreover, it was noted that Hb level was significantly lower in the hyperthyroid group with a mean of 9.6 g/dL. Other biochemical and hematological parameters were similar in both groups. Immunological parameters, virology status, CKD findings in abdomen US, and osteoporosis in DEXA scan did not show any significant difference between the groups.

DISCUSSION

This cross-sectional study examined the relationship between thyroid function test results and various clinical parameters in CKD patients. Thyroid dysfunctions existed in parallel with kidney dysfunction. These hormonal axis dysfunctions may not be apparent at first presentation and may require close clinical and laboratory evaluations. There are several interesting findings including: 1) the high prevalence of thyroid dysfunction (11.7%); 2) high cholesterol and LDL levels in hypothyroid patients; and 3) higher levels of urea in hyperthyroid patients (suggesting greater catabolism).

Thyroid hormone abnormalities have been reported among clinically euthyroid patients with ESKD, including reduced total and free T3 and T4 levels.[2–4,8,9,11] The background for these abnormalities is unclear, however, it has been postulated to be due to adaptive response to chronic non-thyroidal illness, uremia, and protein malnutrition.[5,17] The present study showed that even among newly diagnosed patients with CKD, thyroid dysfunction was present in almost 11.7% of the studied population.

Hypothyroidism was present in two-thirds and hyperthyroidism in one-third of thyroid dysfunction among CKD population. A study from Saudi Arabia reported similar results: hypothyroidism is highly prevalent in Saudi patients with long-term CKD and type 2 diabetes mellitus with a prevalence of 26%.[18] A study from the USA showed that subclinical primary hypothyroidism is relatively a common condition (~18%) among persons with CKD, who were not requiring chronic dialysis and it is independently associated with progressively lower estimated GFR in large cohort of unselected outpatient adults.[19] In addition, a study showed a considerably high prevalence of subclinical hypothyroidism in CKD patients on hemodialysis, especially among females.[20] However, we showed that even at an early stage of CKD, thyroid abnormalities are present among the CKD population. This may get worse with time and contributes to the deterioration of CKD towards ESKD. Therefore, early intervention may ameliorate the progression to end-stage disease.

This study showed that urea was significantly higher in the hyperthyroid group. However, it demonstrated that creatinine levels did not show a statistical difference. Mariani et al,[4] stated that hyperthyroidism is characterized by an increased renal plasma flow and GFR, resulting in reduced serum creatinine levels. The reduction in serum creatinine has also been reported in subclinical hyperthyroidism.[21] Researchers have shown that in hyperthyroidism, the cardiac output is increased, and serum creatine is increased. Thus, serum creatinine concentration was suppressed due to a decrease in creatinine synthesis and an increase in renal creatinine excretion. Blood urea nitrogen (BUN) was high, primarily due to increased urea nitrogen production secondary to excessive protein catabolism together with insufficient excretion of BUN.[22–24]

Our study showed a similar result regarding the increased serum urea level. However, there were some discrepancies compared to international studies regarding serum creatinine level. Another study showed that serum urea is increased, creatinine is decreased, and GFR was increased in hyperthyroidism.[23] Moreover, a regional study from Sudan showed that hyperthyroidism decreases serum creatinine levels slightly and increases serum urea.[25] The reason for this discrepancy between our study and other studies could be due to the different characteristics of the study group as all of our patients are CKD patients with a low mean GFR 21.0±16.5 and the other studies were not done on CKD patients specifically.

Undiagnosed and untreated hypothyroidism poses dangers to CKD patients in many ways. One of the most important factors is that ESKD patients have a well-recognized increased risk of cardiovascular disease that begins early in the course of CKD and results in 10-fold or higher cardiovascular mortality rates after starting kidney replacement therapy.[26–28] Hypothyroidism is also a risk factor for cardiovascular disease, thus adding to the existing risks.[29] However, hypothyroidism is a modifiable risk factor, hence should be recognized and treated on time. In addition, hypothyroidism impairs myocardial function.[30] In CKD patients, cardiac function can be already challenged by fluid overload, overt hypertension, anemia, etc., leading to cardiac failure, and hypothyroidism can worsen the situation.

Many studies showed that hypothyroidism is a risk factor for atherogenic lipid profile, which clearly showed that TC and LDL were higher in hypothyroid patients compared to euthyroid patients. One study showed that the mean TC and LDL cholesterol levels of subjects with TSH values between 5.1 and 10 mIU/L were significantly greater than the corresponding mean lipid level in euthyroid subjects.[29] However, there is controversy whether subclinical hypothyroidism can lead to alteration of lipid profile. A meta-analysis suggested that the serum TC, LDL, and total TG levels were significantly increased in patients with subclinical hypothyroidism compared with euthyroid individuals; the weighted mean differences were 12.17mg/dL, 7.01 mg/dL, and 13.19 mg/dL, respectively. No significant difference was observed for serum HDL; however, they mentioned limitations with the included studies mainly in the control of potential confounding factors.[31] One study done in Iraq regarding the

effect of thyroid hormone on serum cholesterol and albumin showed a significant increase in the rate of cholesterol compared to the control group.[32]

Similarly, our study revealed that TC and LDL were significantly higher in hypothyroid patients than in euthyroid patients, and to be noted that our patients in this group are all having subclinical hypothyroid except one patient with clinical hypothyroidism.

Certainly, hypothyroidism is associated with anemia; approximately 20–60% of patients with hypothyroidism are also diagnosed with anemia. It can have various etiologies and can manifest as normocytic, microcytic, or macrocytic anemia.[33,34] In patients on maintenance hemodialysis, erythropoietin resistance is a common problem, and hypothyroidism should be ruled out together with the other well-known causes.[24] Hyperthyroidism contributes to anemia in CKD patients as well. Hyperthyroidism is considered one of the causes of anemia with resistance to human recombinant human erythropoietin (EPO).[35] Our study showed that Hb level was significantly lower in the hyperthyroid group. It also showed that WBC was higher in hypothyroid patients than those with normal thyroid function, although literature showed that thyroid hormone deficiency results in a decrease in total blood counts, including WBC.[36] The reason for this could be other confounding factors in our study, like the presence of infection at the time of testing.

Thyroid hormone promotes albumin catabolism, thus albumin degradation is reduced in hypothyroidism.[37] One study showed that glycated albumin is spuriously high in non-diabetic patients with overt hypothyroidism.[38] Another study regionally in Iraq regarding the effect of thyroid hormone on serum cholesterol and albumin showed that albumin level did not have a significant difference between the hypothyroid and control group.[32] Contrary to the above studies, our study showed that serum albumin was significantly lower in the hypothyroid group. Our finding is supported by another study that concluded that patients with proteinuria have higher TSH levels, consistent with urinary loss of thyroid hormones.[39] However, our patients have no significant difference in proteinuria between the compared groups. Another study done by Shantha et al,[40] demonstrated similar results to our study that albumin was significantly lower in the hypothyroid group and concluded that decreased level of serum albumin is a risk factor for subclinical hypothyroidism in patients with ESKD.

There are some limitations in this study which needs to be considered. First, this is a single-center study, but it covers the entire country. Second, the study is performed at a single point in time at the initial clinical encounter with CKD diagnosis and did not examine progress over time between different stages of CKD. In addition, we did not compare normal to abnormal structural thyroid abnormalities, but only examined the hormonal abnormalities. Furthermore, we did not obtain similar data in a healthy control group.

CONCLUSION

Thyroid dysfunction is not uncommon in patients with early CKD, and the most encountered abnormality is subclinical hypothyroidism. Hence, a proper clinical evaluation of thyroid disorders among CKD patients is important. However, more research is needed, especially intervention studies to ascertain that proper management of thyroid status may ameliorate CKD progression towards end-stage disease.

Disclosure

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