Original article

Thyroid dysfunction and iodine status in children with non-dialysis-dependent chronic kidney disease.

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ABSTRACT

Introduction: Thyroid dysfunction in chronic kidney disease (CKD) has been an emerging issue in the last few years. Many literatures demonstrate the relationship between chronic kidney disease and hypothyroidism in adult patients while data in Pediatric cases are scares.

Aim of the study: This cross-sectional study was done to detect the abnormalities of thyroid function and iodine status in children with non-dialysis-dependent CKD.

Methods: The study included 60 patients aged 2.9–16 years fulfilling the diagnostic criteria of CKD. They were subjected to full clinical assessment, estimation of glomerular filtration rate (eGFR), and thyroid function. Serum and urinary iodine levels were estimated in patients and comparable controls.

Results: Showed that 18.2% of the cases had hypothyroidism (3.3 % had primary hypothyroidism, 3.3% had secondary hypothyroidism, 11.6% had subclinical hypothyroidism and 10% of the cases had a nonthyroidal illness (low FT3 and normal TSH levels)). There were significantly higher levels of serum iodine and a significantly lower level of urinary iodine in cases with CKD compared with controls. No significant correlation between either serum or urinary levels of iodine and eGFR or TSH, FT4, or FT3 levels was found. Patients with eGFR < 60 mL/min/1.73m^2 have significantly lower levels of FT3 and FT4 levels than those with GFR ≥ 60 mL/min/1.73m^2. A significant positive correlation between TSH level and creatinine level and a negative correlation between FT3 and creatinine level had been found.

Conclusion: This study confirms the occurrence of changes in thyroid function in pediatric patients with predialysis CKD nearly as that occurs in adult CKD patients.

Keywords: Thyroid dysfunction, iodine status, CKD

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Introduction

Chronic kidney disease (CKD) is a common condition with various health consequences especially in children. Studies showed that patients with CKD had a higher risk of death and a higher risk of hospitalization compared with their non-CKD counterparts **[1].** Thyroid disorders, which are prevalent in CKD patients, have been reported to be a risk factor for death **[2].**

The interplay between the thyroid and the kidney in each other's function has been observed for many years. Thyroid dysfunction affects renal blood flow and glomerular functions, whereas kidney disease could result in thyroid dysfunction. Reduction in T_3 levels (low T_3 syndrome) is the most frequently observed thyroid alteration in these patients, and a higher prevalence of primary hypothyroidism, both overt and subclinical, was recorded **[3].** The prevalence of primary hypothyroidism, mainly in the subclinical form, increases as the glomerular filtration rate (GFR) decreases **[4].** While the mechanism of impaired thyr0id function in patients with CKD is suggested to be multifactorial, including autoimmune hypothyroidism, impaired hypothalamic-pituitary-thyroid tract, or defective peripheral deiodination, the exact mechanism is still unclear. The defect in renal handling of iodine has emerged as an etiologic factor in the increased prevalence of goiter and hypothyroidism reported in CKD. It has been claimed that restriction of dietary iodine can correct hypothyroidism and avoid the need for hormone replacement with levothyroxine **[5]**

Little is known about thyroid dysfunction in pediatric CKD patients and its relation to kidney function. Impaired iodine metabolism and its relation to GFR on the one hand and its relation to thyroid dysfunction on the other hand in these patients are not known.

Aim of the work: To find out the abnormalities of the thyroid function and the iodine status in serum and urine of children with non-dialysis-dependent chronic kidney disease and its relation to thyroid function and glomerular filtration rate.

Methods

This study earned the approval of the Ethics and Research Committee of Assiut University with IRB number: 17300975. Parents and patients agreed to participate in the study and signed a letter of informed consent. All children aged 2 to 18 years fulfilling the diagnostic criteria of CKD were included in the study. A comparable group of age and sex-matched healthy children from the same geographic area were enrolled as controls.

Exclusion criteria:

1. Patients started hemodialysis or peritoneal dialysis.
2. Heavy proteinuria > 3000 mg/day.
3. Patients on drugs that could contribute to hypothyroidism (lithium, amiodarone).
4. Patients had a history of using iodine-containing drugs, contrast, or nuclear studies containing iodine.

For all patients: age, sex, weight, height, and the stage of sexual maturity using the Tanner scale were recorded. The nutritional status was evaluated according to the weight for age, height for age, and weight for height Z scores. Serum urea and creatinine, 24-hours urinary protein excretion, and albumin/creatinine ratio were done. Complete blood count, serum

Na+, K+, Ca+, and Ph+ were estimated. The glomerular filtration rate was estimated using the Schwartz equation [6]

Samples:

1- Six ml of venous blood was collected from patients and control subjects on two plan tubes and left standing until clotting, then centrifuged at 3000 rpm for 20 min and serum was separated and divided into 3 aliquots:

- One for routine parameter estimation (glucose, renal, liver function tests, and calcium) and thyroid function tests; TSH, fT3, and fT4; all parameters have been done on a fully automated chemistry analyzer BT-3500 (Italy). No serum thyroid peroxidase antibody measurements were available.
- The other 2 divisions had been frozen at – 20℃ for later use for estimation of serum Iodine level.

2- Urine samples had been collected and centrifuged for 20 min at 1000 rpm (to separate the debris) and supernatant had been collected and stored at – 20℃ for later use for estimation of urinary Iodine level.

Human Iodine estimation kits in body fluids: By Sandwich ELISA technique BIM, Kenneth G. Howell, 748 Nickel Road, San Francisco (415), CA 94104 Principle of the Iodine estimation kits: Kits adopted on coated microtiter plate with iodine, make solid-phase antibodies, and then add iodine to wells (samples). Combine iodine antibody with labeled HRP to form antibody-antigen-enzyme-antibody complex, after washing completely, add TMB substrate solution. TMB substrate becomes blue color at HRP enzyme-catalyzed, reaction is terminated by the addition of a stop solution, and the color change is measured at a wavelength of 450 nm. The concentration of iodine in the samples is then determined by comparing the optical density (OD) of the samples to the standard curve.

Operational definitions:

Chronic kidney disease: The presence of markers of kidney damage for at least three months, as defined by structural or functional abnormalities of the kidney with or without a decreased GFR that is manifested by either pathological abnormalities or other markers of kidney damage, including abnormalities in the blood, urine, or in imaging tests or GFR below 60 ml/min/1.73m^2 for at least three months, with or without kidney damage.

Nondialysis dependent chronic kidney disease: patients with an established CKD who do not yet require the life-supporting treatments for kidney failure known as renal replacement therapy including maintenance dialysis or kidney transplantation.

Thyroid function interpretation:

Euthyroidism: is defined as levels of fT3, fT4, and TSH within the normal ranges; which is considered as 0.5 - 4.06 μIU/ml for TSH; 0.89 - 1.8 ng/ml for FT4; and 78 -182 ng/ml for FT3.

Subclinical hypothyroidism; is characterized by TSH between 4.07 and 9.9 μIU/ml and normal T3 and T4 levels,

Primary hypothyroidism: is defined by levels of TSH > 10 μIU/ml and T3 and T4 below normal levels.

Secondary hypothyroidism is defined as TSH and fT4 below normal levels

Non-thyroidal illness (Euthyroid Sick Syndrome) is characterized by a decrease in free T3 concentration, whilst TSH level is normal and finally,

Hyperthyroidism is defined as low TSH and high FT4 and FT3.

STATISTICAL ANALYSIS

Collected data were coded, analyzed, and computed, using the IBM® SPSS® Statistics Version 26 for Windows. The data were tested for normality using Kolmogorov-Smirnov and Shapiro-Wilk tests and showed non-parametric (not normal) distribution. Categorical variables were described by number and percent (N, %), whereas continuous variables were described by mean and standard deviation (Mean, SD). The Chi-square test and Fisher exact test were used to compare categorical variables where compare between continuous variables Kruskal Wallis test was used to compare more than two groups in non-related samples, and Mann Whitney was used to compare two groups in non-related samples. We used the Pearson test for correlation coefficients. The significance level was set at $P \leq 0.05$. **Computer software** performed using the Statistical Package for Social Sciences (SPSS) 23.0 software program (SPSS Inc., Chicago, IL, USA).

RESULTS

Sixty patients fulfilling the diagnostic criteria of predialysis chronic kidney disease were enrolled from the Nephrology Unit and outpatient clinic of Assiut University Children Hospital.

The patients were 38 males (63.3%) and 22 females (36.7%) with a mean age of 9.87±3.59 years, range of 2.9 – 16 years. The demographic characteristics, etiology of CKD, and the abnormalities of thyroid function in the studied cases are shown in **Table 1.**

Table 2 shows the anthropometry, thyroid function, and iodine status of the studied CKD patients compared with the control. There were significantly higher levels of serum iodine and significantly lower levels of urinary iodine in the studied cases of CKD compared with controls. However there was no significant correlation between either serum or urinary levels of iodine and eGFR or TSH, FT4, or FT3 levels.

Table 3 shows the studied laboratory data in CKD patients with GFR ≥ 60 mL/min/1.73m^2 compared with those with GFR < 60 mL/min/1.73m^2. The latter group has significantly lower levels of FT3 and FT4 levels than the former group. Although there was no significant correlation between TSH, fT4, and fT3 with the eG23FR, there was a significant positive correlation between TSH level and creatinine level and a negative correlation between FT3 and creatinine level **Figure 1**.

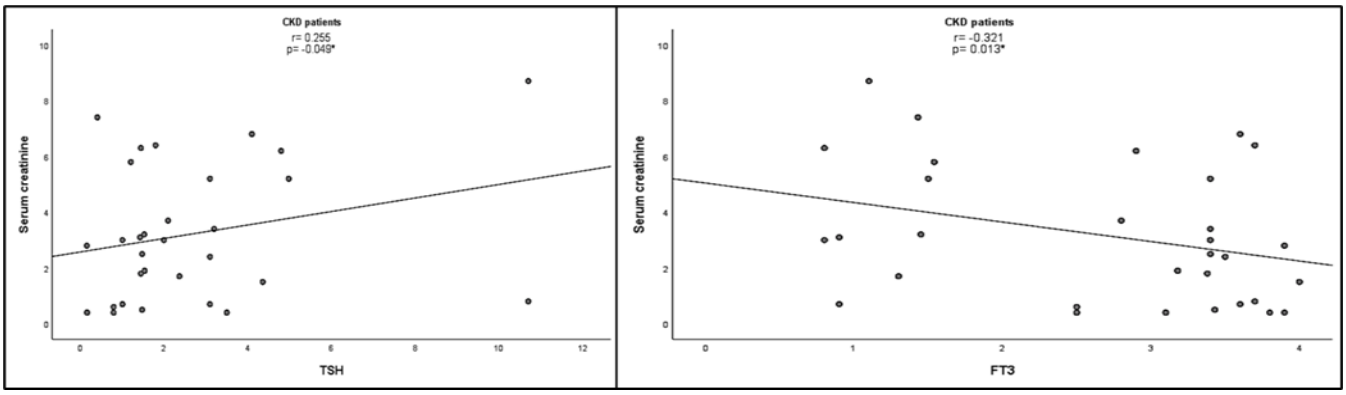

Figure 1: Correlation between serum creatinine level and TSH level (left) & FT3 (right

Table 1: Demographic Characteristics, etiology of CKD, eGFR and the pattern of thyroid function in the studied CKD patients.

Parameter	Result
Age (years): range Mean ± SD	2.9 - 16 9.87±3.59
Sex: Males Females	38 (63.3%) 22 (36,7%)
Etiology of the CKD:	
• Chronic glomerulonephritis	20 (33.3%)
• Vesico-ureteric reflux	13 (21.6%)
• Nephrolithiasis	9 (15.0%)
• Lupus nephritis	9 (15.0%)
• Hereditary nephritis	3 (5.0%)
• Laurance-Moon Beidle syndrome	3 (5.0%)
• Polycystic kidney	2 (3.33%)
• Unilateral renal agenesis with contralateral hypoplasia	1 (1.66%)
Estimated glomerular filtration rate (mL/min/1.73m^2):	
• ≥ 90	8 (13.3%)
• 60-89	6 (10.0%)
• 45-59	2 (3.3%)
• 30-44	1 (1.7%)
• < 30	43 (71.7%)
Pattern of thyroid function:	
• Euthyroidism	40 (66.6%)
• Subclinical hypothyroidism	7 (11.6%)
• Primary hypothyroidism	2 (3.33%)
• Secondary hypothyroidism	2 (3.33%)
• Non-thyroidal illness	6 (10.0%)
• Hyperthyroidism	3 (5.0%)

Table 2: Anthropometry, thyroid function and iodine status of the studied CKD patients compared with the control.

		Cases (n=60)	Controls (n=60)	P. value
Weight (kg)	Range Mean±SD	9 - 75 28.63±14.99	10 - 79 34.35±15.09	**0.024***
Height (cm)	Range Mean±SD	90 - 166 122.38±22.29	95.5 - 161 132.38±17.18	**0.010***
BMI (kg/m^2)	Range Mean±SD	8.65 - 36.68 18.12±5.77	10 - 32.15 18.59±4.39	0.299
TSH (μIU/ml)	Range Mean±SD	0.16 - 10.7 2.66±2.53	0.4 - 6.6 2.85±1.49	0.440
FT3 (ng/ml)	Range Mean±SD	0.8 - 4 2.62±1.11	1.27 - 294 12.5±52.72	0.606
FT4 (ng/ml)	Range Mean±SD	0.89 - 2.1 1.29±0.33	0.7 - 9.3 1.58±1.24	0.405
Serum iodine (ng/ml)	Range Mean±SD	71.2 - 115.3 88.86±12.91	0.5 - 59 34.93±20.16	**<0.001****
Urinary iodine (ng/ml)	Range Mean±SD	17.8 - 46.4 31.91±6.84	0.56 - 156 56.2±42.37	**0.043***

Table 3: Thyroid function tests and iodine in the studied patients with CKD according to eGFR

		eGFR		P. value
		≥60 (n=14)	<60 (n=46)	
TSH (μIU/ml	Range Mean±SD	0.16 - 10.7 2.94±3.5	0.16 - 10.7 2.58±2.2	0.452
FT3 (ng/ml	Range Mean±SD	2.5 - 3.9 3.24±0.54	0.8 - 4 2.43±1.18	**0.029***
FT4 (ng/ml)	Range Mean±SD	1.04 - 2.1 1.41±0.36	0.89 - 2.1 1.25±0.32	**0.044***
Serum iodine (ng/ml)	Range Mean±SD	7.3 - 52.4 35.76±14.53	0.5 - 59 34.67±21.72	0.612
Urinary iodine (ng/ml)	Range Mean±SD	14 - 96.6 49.24±33.2	0.56 - 156 58.32±44.89	0.675
Pattern of Thyroid function:	- Euthyroid - Hypothyroidism - Non-thyroidal illness - hyperthyroidism	11(78.6%) 1 (7.1%) 0 (0.0%) 2 (14.3%)	30 (65.2%) 9 (19.5%) 6 (13.1%) 1 (2.2%)	0.100

DISCUSSION

This study included 60 pediatric patients fulfilling the diagnostic criteria of CKD who were not on dialysis. On assessing their thyroid function, it was found that 18.2% had hypothyroidism of various types. Connie et al [7] found nearly a quarter of their studied series of adult patients with CKD had hypothyroidism. Rhee et al [8] studied 461,607 US veterans with stages 3 to 5 CKD who underwent serum TSH testing. They found that 23% of them had hypothyroidism. The present result in pediatric CKD patients is near that reported in adult CKD patients indicating that the underlying pathophysiologic process could be the same irrespective of the age of patients. The high prevalence of thyroid disorder associated with chronic kidney disease has been suggested to be either a physiological adaptation of thyroid function to CKD or it may reflect extrarenal complications of metabolic nature [9].

Out of the present cases of CKD with hypothyroidism; 3.3 % had primary hypothyroidism, 3.3% had secondary hypothyroidism, and 11.6% had subclinical hypothyroidism **Table 1**. These variable types of CKD-associated hypothyroidism suggest different pathophysiologic mechanisms including suppression of the hypothalamic-pituitary-thyroid axis or changes in peripheral hormone metabolism and thyroid hormone binding proteins [10]. Subclinical hypothyroidism, which is an elevation in serum TSH level with a normal serum free-T4 concentration, represents 11.6% of the present studied cases with CKD as a whole, and 63.6% of CKD-associated hypothyroid cases. Lo et al [11] reported that patients with end-stage kidney disease had a prevalence of hypothyroidism of 7.94 % of whom 89% had evidence of subclinical hypothyroidism, while Chonchol et al [4] showed that approximately 18% of the patients with non-dialysis dependent CKD have subclinical primary hypothyroidism, a finding that is independently associated with a progressively lower estimated GFR. Our result in pediatric CKD patients is in accordance with these results reported in adult CKD patients.

Another 10% of the studied cases with CKD had a nonthyroidal illness (low FT3 and normal TSH levels) **Table 1.** It has been reported that the earliest and the most common thyroid function abnormality in CKD patients is a low T3

level; "low T3 syndrome" [12] which results from a decrease in peripheral conversion of T4 to T3 as a result of several factors as fasting, chronic metabolic acidosis, chronic protein malnutrition and impaired renal handling of iodine that may affect iodothyronine deiodination [5]. This thyroid profile is similar to that observed in several non-thyroidal illnesses such as severe infections, heart failure, and malignancies, and in several hospitalized patients without renal disease. Traditionally, a decrease in plasma T3 concentration is an attempt to conserve body energy stores by reducing metabolic rate, e.g. in periods of starvation [13]. On the other hand, low T3 could be associated with pathological conditions and maladaptation leading to decreased survival rather than a sign of physiological adaptation to energy shortage [14].

In the present study, CKD patients with eGFR ≥ 60 mL/min/1.73m^2 had significantly higher fT3 and fT4 levels than patients with eGFR levels < 60 mL/min/1.73m^2. Furthermore, 19.5% of pediatric patients with eGFR < 60 mL/min/1.73m^2 had hypothyroidism compared to 7.04% of patients with eGFR > 60 mL/min/1.73m^2 **Table 3**. Lo *et al*. [11] noticed that the prevalence of subclinical and clinical primary hypothyroidism increased with progressively lower levels of kidney function in a nationally representative cohort of US adults. Among these participants, more than 20% of those with an estimated GFR <60 ml/min per 1.73 m^2 had clinical or subclinical primary hypothyroidism after controlling for age, gender, and race/ethnicity.

The Third National Health and Nutritional Examination Survey (NHANES III) [15] showed that there was an incrementally higher prevalence of hypothyroidism with increasing severity of kidney dysfunction: 5, 11, 20, 23, and 23% with eGFRs of ≥90, 60–89, 45–59, 30–44, and <30 ml/min/1.73m^2, respectively. Even after accounting for differences in age, sex, and race/ethnicity, participants with eGFRs <30 ml/min/1.73m^2 had a 2-fold higher risk of hypothyroidism compared to those with eGFRs >90 ml/min/1.73m^2. In this NHANES III study, 56% of hypothyroid cases were due to subclinical disease.

Connie et al [7] found a significant association between eGFR and risk of hypothyroidism independent of age, sex, race, and comorbidity status. The incidence of subclinical primary hypothyroidism increased from 7% to 17.9% in 3089 ambulatory adults in Italy whose GFR has decreased from ≥90 mL/min to 60 mL/min [4]. Even a population-based study of 29480 individuals older than 40 years has demonstrated an inverse association between eGFR and serum TSH levels and/or risk of hypothyroidism [16]. However, in the present study, no significant correlation was found between eGFR and serum TSH, fT4, or fT3 levels, whereas there was a significant positive correlation between serum creatinine and TSH level as well as a significant negative correlation between serum creatinine and fT3 level **Figure 1**.

Srivastava et al [17] found significant inverse moderately strong correlation between the blood urea and free thyroid hormones as well as between serum creatinine and free thyroid hormones. There was no significant positive correlation between the blood urea values and TSH, with just a significant positive correlation between the serum creatinine and TSH. The significant correlation between thyroid function with blood urea

nitrogen rather than the eGFR raises the question of whether hypothyroidism is a result or a cause of the reduction of kidney function.

The present study shows that there were significantly higher levels of serum iodine and a significantly lower level of urinary iodine in the studied cases of CKD compared with controls **Table 2**. However, no significant correlation was found between eGFR and either serum or urinary iodine levels. Furthermore, no significant difference was found between patients with higher eGFR (≥ 60 mL/min/1.73m^2) and those with lower eGFR (< 60 mL/min/1.73m^2) regarding serum or urinary iodine **Table 3**. Avasthi et al **[18]** studying 30 patients who had chronic renal failure (CRF) aged 22-70 years showed that there was no significant difference in the mean values of serum organic iodine levels in cases versus controls; (CRF patients 0.87±0.32ug/dl, controls 0.88±0.23ug/dl;p>0.05), whereas the urinary excretion of iodine was significantly decreased in patients of CRF as compared to normal controls (CRF 1 6.33±3.54ug/100ml; controls 33.10±21.90ug/100ml p<0.05). They found significantly lower FT4 and significantly higher TSH levels in patients than in control. These results do not differ according to the severity of renal impairment.

The kidney contributes to the iodine clearance primarily through glomerular filtration. It has been proposed that CKD results in reduced iodide excretion, which causes the inorganic iodide generated by residual deiodinase activity accumulate in the blood and results in increased thyroid gland iodine which can potentially block thyroid hormone production causing a prolonged Wolff – Chaikoff effect **[12,19].** Moreover, no significant correlation was found between iodine levels and thyroid function in the studied cases of CKD. Failure to find a direct relation between iodine level and thyroid function may raise the possibility that excess iodine may enhance the development of hypothyroidism in CKD patients due to other mechanisms.

CONCLUSION

This study confirms the occurrence of abnormalities in thyroid function in pediatric patients with predialysis CKD nearly as that occurs in adult CKD patients. The relation of these changes to eGFR is not well confirmed. Serum iodine concentrations are high in CKD but are not correlated with the degree of kidney failure or thyroid dysfunction. Further longitudinal studies on a larger number of patients are recommended to delineate the possible etiology of these relations.

LIMITATIONS OF THE STUDY

Although this study was carried out on a considerable number of pediatric predialysis CKD patients, had some limitations in that it is a cross-sectional study, so causality cannot be established. Furthermore, there were a smaller number of cases representing various degrees of impaired renal function.

ABBREVIATIONS

+Ca	Calcium
CKD	chronic kidney disease
FT3	Triiodothyronine
FT4	Tetraiodothyronine
eGFR	estimation of glomerular filtration rate
GFR	Glomerular filtration rate
K	Potassium
m2	Meter square
min	Minute
mL	Milliliter
mg	Milligram
+ Na	Sodium
OD	Optical density
Ph+	Phosphorus
TSH	Thyroid stimulating hormone

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AUTHORS' CONTRIBUTIONS

The submitted manuscript is the work of the author & co-author.

All authors have contributed to authorship, have read and approved the manuscript.

STATEMENTS

Design of study: cross sectional study
Data collection had been done by the authors.

Ethics approval and consent to participate
This study protocol and the consents were approved and deemed sufficient by the Ethical Committee of Assiut University. Parents and patients agreed to participate in the study and signed a letter of informed consent.

Consent for publication
The contents and material of the manuscript have not been previously reported at any length or being considered for publishing elsewhere.

Availability of data and material :
"Not applicable"

Conflict of interest
The authors declare no conflict of interest.

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