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PROSPECTIVE STUDY OF THYROID FUNCTIONS IN CHILDREN WITH CHRONIC KIDNEY DISEASE

Paediatric Medicine

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ABSTRACT

Nephro-endocrine association has been known for a long time. The kidney contributes to clearance of iodine primarily by glomerular filtration. As iodine excretion is diminished in advanced renal failure, leading to an elevated plasma inorganic iodide concentration and initial increment in throidal iodide uptake. Increased total body iodide can potentially block thyroid hormone production by affecting the pituitary-thyroid axis and peripheral metabolism of thyroid hormone .So, thyroid dysfunction is commonly seen endocrine abnormality among CKD patients. It has been shown that in CKD, as the GFR falls there is a higher possibility of developing clinical and subclinical hypothyroidism.

KEYWORDS

Subclinical Hypothyroidism, Chronic Kidney Disease,

INTRODUCTION :

Chronic kidney disease (CKD) is a major health problem worldwide with increasing incidence and prevalence that is threatening to bring on the onset of a real 'epidemic'. In children, it can be a devastating illness with many long-term consequences. Independent of the initial cause, CKD is a clinical syndrome characterized by a gradual loss of kidney function over time. In particular, the Kidney Disease Improving Global Outcomes (KDIGO) guidelines have defined CKD as abnormalities of kidney structure or function, present for more than 3 months. The interplay between thyroid and the kidney in each other's functions is known for many years.[1] Thyroid dysfunction affects renal physiology and development, whereas kidney disease could result in thyroid dysfunction. Disorders of the thyroid and kidney may co-exist with common etiological factors. The kidney normally contributes to the clearance of iodide, primarily by glomerular filtration. Thus, iodide excretion is diminished in advanced renal failure, leading sequentially to an elevated plasma inorganic iodide concentration and an initial increment in thyroidal iodide uptake. The ensuing marked increase in the intra thyroidal iodide pool results in diminished uptake of radio labeled iodide by the thyroid in uremic patients.[2] Increases in total body inorganic iodide can potentially block thyroid hormone production (the Wolff-Chaikoff effect). Such a change may explain the slightly higher frequency of goiter and hypothyroidism in patients with chronic kidney disease.[3]Thyroid functional disorders are commonly observed in chronic kidney disease (CKD) patients, various thyroid functional test abnormalities are frequently seen in CKD patients, resulting from alterations in thyroid hormone synthesis, metabolism, and regulation. . The relation between thyroid dysfunction and severity of CKD is not clear. Several previous studies depict conflicting results both positive and negative. Thus, there are huge numbers of patients remaining to be diagnosed and/or treated.Hence the present study was done at our tertiary care centre to study the prevalence of abnormal thyroid functions in children with chronic kidney disease and correlate abnormal thyroid functions with different etiologies of chronic kidney disease and different stages of chronic kidney disease.

Literature survey:

Etiology of CKD in children

Frequency of different diagnostic groups as causes of CKD and ESRD in children

	Frequency as cause of CKD	Aetiology	Proportion of cases of CKD determined by specific diagnostic sub-groups	Frequency as cause of ESRD
Glomerular diseases	6.8–20.5 %	SRNS	10.4%	15.2–24.3%
		Glomerulonephritis	8.1%	
		Thrombotic microangiopathies (aHUS)	2.0%	
Structural and other	56–57.6 %	CAKUT	49.1%	38.3–39.5%
		Ciliopathies	5.3%	
		Nephrolithiasis, nephrocalcinosis	1.6%	

The distribution of the frequency shows that different aetiologic groups are differentially responsible for CKD and ESRD, mainly because of the different rate of progression towards ESRD of the different diagnostic categories (e.g. glomerular versus structural).

CKD, chronic kidney disease; ESRD, end-stage renal disease; CAKUT, congenital abnormalities of kidney and urinary tract; SRNS, steroid-resistant nephrotic syndrome; aHUS, atypical haemolytic uraemic syndrome.

Hypothyroidism: A Common Yet Under-Recognized Endocrine Disorder in Kidney Disease

While a greater emphasis has been placed upon other endocrine disorders in CKD (e.g., secondary hyperparathyroidism, diabetes), large observational studies show that hypothyroidism is highly prevalent in kidney disease patients. Even after accounting for differences in age, sex, and race/ethnicity, participants with eGFRs <30 ml/min/1.73m2 had a 2-fold higher risk of hypothyroidism compared to those with eGFRs >90 ml/min/1.73m2. In a study of 3089 ambulatory adults in Italy, it was also found that there was an increasingly higher prevalence of subclinical hypothyroidism with lower levels of kidney function: 7 vs. 18% with eGFRs ≥90 vs. <60 ml/min/1.73m2, respectively.[6]

A high prevalence of hypothyroidism has also been observed in dialysis patients, albeit in comparatively smaller-sized cohorts. In US and Asian hemodialysis and peritoneal dialysis cohorts, the prevalence of hypothyroidism has ranged from 13 to 25%. Despite these data, hypothyroidism remains under-recognized in many advanced CKD patients, likely due to symptom overlap with uremia (e.g., fatigue, cold intolerance, decreased cognition).

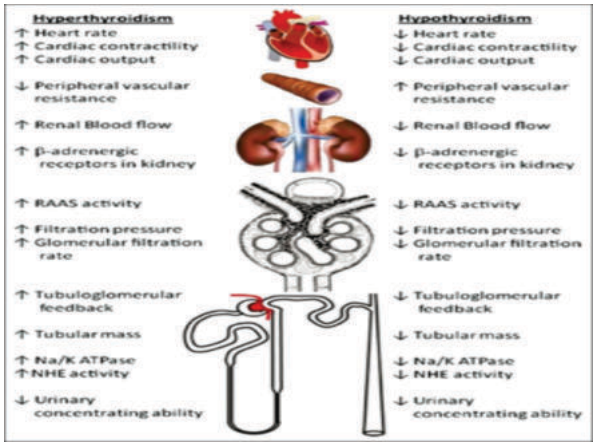
Interactions between thyroid disorders and kidney disease

Effects of Thyroid Hormones on Renal Development

Thyroid hormones influence protein synthesis and cell growth. Thyroid hormone status affects the functioning renal mass (measured as the kidney to body mass ratio), with hypothyroidism reducing this ratio and hyperthyroidism increasing it. However, severe hyperthyroidism results in protein breakdown and eventual renal atrophy. In addition, children with congenital hypothyroidism have a high incidence of congenital renal anomalies. Thyroid hormones also influence the neonatal renal function. Perinatal thyroid hormone status affects the mitochondrial energy metabolism enzymes in the cells of the proximal convoluted tubules (PCT).[7]There is an increase in the activity of the Na – P co-transporter (NaPi), Na – H exchanger (NHE), as well as the Na/K ATPase in the PCT. Thus, thyroid hormones play an important role in renal development and early renal function.

Effects of Thyroid Dysfunction on the Kidney

Effects of hyperthyroidism and hypothyroidism on Clinical effects of hypothyroidism and hyperthyroidism on renal function tests renal physiology and function



Tests	Hypothyroidism	Hyperthyroidism
Serum creatinine	Increased	Decreased
Serum cystatin C	Decreased	Increased
Urinary NGAL	Unchanged	Unchanged
24-hour urine protein	Increased	Increased
Water load excretion	Decreased	Increased
Electrolyte imbalance	Hyponatremia	None

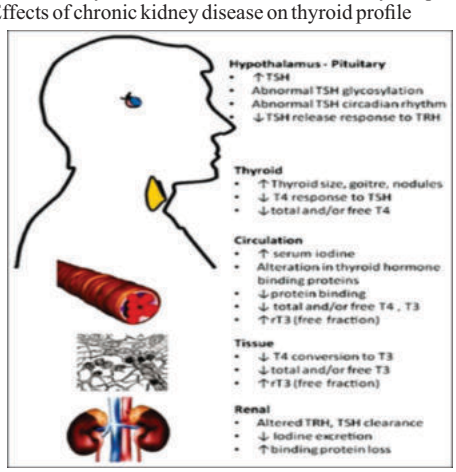
Chronic Kidney Disease and Thyroid Dysfunction

Hyperthyroidism can result in/accelerate chronic kidney disease (CKD) by several mechanisms. Firstly, hyperthyroidism results in intra-glomerular hypertension (increased filtration pressure) and consequent hyperfiltration. Secondly, hyperthyroidism predisposes to proteinuria, which is known to cause direct renal injury. Thirdly, hyperthyroidism-induced increased mitochondrial energy metabolism along with down-regulation of superoxide dismutase contributes to the increased free radical generation and consequent renal injury. Oxidative stress also contributes to hypertension in hyperthyroidism, which contributes to CKD progression. The increased RAAS activity can accelerate renal fibrosis. Primary hypothyroidism (non-autoimmune) is commonly observed in CKD patients. Especially, the prevalence of subclinical hypothyroidism increases consistently with decline in GFR. The earliest and the most common thyroid function abnormality in CKD patients is a low T3 level (especially total T3 than free T3). This "low T3 syndrome" occurs in CKD due to several reasons. Fasting, chronic metabolic acidosis and chronic protein malnutrition affect iodothyronine deiodination, as well as protein binding of T3, reducing the peripheral conversion of T4 to T3 and its protein binding. In addition, inflammatory cytokines such as tumor necrosis factor (TNF)-α and interleukin (IL)-1 inhibit the expression of type 1 5'-deiodinase, which is responsible for peripheral conversion of T4 to T3. In addition, impaired renal handling of iodine increases serum iodine levels, causing a prolonged Wolff – Chaikoff effect. The clinical importance of this low T3 syndrome is controversial. The low T3 levels (especially total T3 and not free T3) in CKD patients have been correlated with higher levels of markers of inflammation [highly sensitive C-reactive protein (hsCRP), IL-6, etc.], malnutrition (lower prealbumin, IGF-1), increased endothelial dysfunction, poorer cardiac function, poor survival, and higher all-cause as well as cardiovascular mortality in some studies. In some other studies, the low free T3 and not the total T3 level is associated with increased mortality. However, recent studies have demonstrated that this association is not invariable, and the free T3 levels may not be associated with long-term mortality in CKD and dialysis patients.[13]

Subsequent studies also demonstrated a low T4 level in many CKD patients. However, the free T4 levels vary from being low to normal in CKD. This is primarily because of an impaired protein binding of T4 in CKD. The thyroid profile is similar to that observed in several non-thyroidal illnesses (NTIs) such as severe infections, heart failure, malignancies, and in several hospitalized patients without renal disease. This led to the consideration of a "sick euthyroid state" in CKD, which is now called "non-thyroidal illness." However, unlike other NTI states, there is no increase in total rT3 levels in CKD.[60] This is due to an increased redistribution of rT3 into extravascular and intracellular spaces. In some patients, due to an impaired renal clearance, free rT3 levels may be mildly elevated. Another difference from other NTIs is that the thyroid stimulating hormone (TSH) levels are elevated in CKD. However, TSH is released in response to thyrotropin releasing hormone (TRH) in CKD patients, indicating pituitary disturbances in uremia. In addition, the circadian rhythm of TSH and its glycosylation is altered in CKD, compromising its activity. Thus, CKD patients have low T3 and normal or reduced T4 levels, and consequently elevated TSH and attendant increase in thyroid gland volume.

These mechanisms are probably reflective of the physiological adaptation of the body to CKD to reduce the protein nitrogen turnover, reduce the protein catabolism and nitrogenous waste load. The reduced T3 levels and associated complications without increase in rT3, the reduced free T4 levels along with an elevated TSH, and hyporesponsiveness of TSH to TRH question the "euthyroid" state and raise the possibility of benefit from thyroid supplementation CKD. However, three decades of research in this area have not been able to clarify the need for thyroid hormone replacement in CKD. Attempts at T3 replacement have often resulted in negative nitrogen balance by increased muscle catabolism, implying the prudence in not correcting the low T3 state in CKD. Though it is clear that hypothyroidism would threaten the patient's well-being, it is not clear as to what level of thyroid dysfunction forms the threshold necessary for treatment by thyroxine replacement in CKD. In general, mild elevations of TSH (less than 20 IU/ml) with or without low T3/T4generally do not warrant thyroid hormone supplementation. One has to consider the dangers of hyperthyroidism as well as the teleological benefits of a hypothyroid state in CKD and the lack of clearly evident benefits of thyroid hormone replacement in the literature before deciding on therapy. A clinical decision of the treating nephrologists and endocrinologists should be made on an individual patient basis, after carefully considering the clinical features, possible hypothyroid manifestations, putative benefits, and possible risks of thyroid hormone therapy or the lack of it.

CKD results in reduced iodide excretion, which results in increased serum inorganic iodide level and the thyroid gland iodine content and consequent thyroid gland enlargement. There is no increase in the incidence of autoimmune thyroid disease in CKD patients. In fact, the incidence of positive thyroglobulin and thyroid microsomal antibodies is low in CKD patients. However, autoimmune thyroid disease may occur along with other autoimmune diseases associated with CKD, such as lupus nephritis, type 1 diabetes mellitus, etc. When elevated TSH is detected in association with other autoimmune disease, it is important to screen for antithyroid antibodies. Management strategy for autoimmune thyroid disease remains unaltered by the presence of CKD. Effects of chronic kidney disease on thyroid profile



Mechanistic Links between Thyroid and Kidney Disease

Thyroid Functional Disease as a Risk Factor for Kidney Disease

While the mechanistic link between thyroid and kidney disease remains unclear, animal studies have demonstrated that hypothyroidism adversely affects kidney size and structure in both development and adulthood.[13] In neonatal rats, hypothyroidism has resulted in reduced kidney-to-body weight ratio, truncated tubular mass, and various glomerular basement membrane (GBM) changes (e.g., reduced GBM volume and area, GBM thickening, mesangial matrix expansion, and increased glomerular capillary permeability).[56] It has also been suggested that hypothyroidism leads to kidney

dysfunction, vis-à-vis several potential mechanisms, including (1) decreased cardiac output, (2) altered intra-renal hemodynamics (i.e., intra-renal vasoconstriction resulting from decreased vasodilator synthesis and activity), (3) reduced renin-angiotensin-aldosterone production and activity, and (4) increased tubulo-glomerular feedback due to alterations in chloride channel and expression. Indeed, in animal studies, induction of hypothyroidism by thyroidectomy has resulted in reduced single nephron glomerular filtration rate, renal plasma flow, and glomerular transcapillary pressure. Multiple case series have also shown that severe hypothyroidism results in creatinine elevations, reduced plasma flow, and decreased GFR as ascertained by indirect estimating equations, and gold standard isotopic scans; in these reports, creatinine elevations and reductions in GFR were reversed with exogenous thyroid hormone replacement.

Chronic Kidney Disease as a Risk Factor for Thyroid Dysfunction

Conversely, patients with CKD may be at higher risk for thyroid dysfunction via several suggested pathways. For example, iodine retention due to impaired kidney excretion has been hypothesized as a possible mechanism for hypo- and hyperthyroidism in CKD via the Wolff-Chaikoff effect and Jod-Basedow phenomenon, respectively. Several case reports and series have reported iodine-associated hypothyroidism among adult and pediatric dialysis patients consuming high iodine diets (e.g., seaweed), exposure to povidine-iodine cleansing agents, and receipt of iodine-contrast media enhanced angiography. While several recent observational studies have shown that iodinated contrast media is associated with higher risk of incident hypothyroidism and hyperthyroidism, a more potent association in those with vs. without kidney dysfunction has not been observed.[16] Patients with CKD may frequently have metabolic acidosis, which has been shown to result in thyroid functional test alterations (elevated TSH and low T4 and triiodothyronine [T3]) levels, partially improved with oral sodium citrate therapy. Selenium is an important trace mineral in the human diet that modulates the peripheral conversion of T4-to-T3 by controlling iodothyronine deiodinase activity.

Methodology:

AIMS AND OBJECTIVE:

1) To study the prevalence of abnormal thyroid functions in children with chronic kidney disease.
2) To correlate abnormal thyroid functions with different etiologies of chronic kidney disease and different stages of chronic kidney disease

Study design: A hospital based prospective observational study
Study Duration: 18 months
Study area: The study was done at our tertiary care centre in the department of Pediatrics, OPD of BJWCH on attending
Study population: All CKD children attending the OPD of BJWCH and newly diagnosed CKD children admitted in ward or coming in the OPD after metabolic stabilization at our Tertiary care Hospital who fulfilled the inclusion criteria.
Sample size: 66 patients

Sample size was calculated using the formula:

$n= [z^2 p(1-p)]/d^2$

Where: Z = table value of alpha error from Standard Normal Distribution table (0.95)
Power (p) = 80%
Precision error of estimation (d) = 4.75%
n= [0.95 x 0.95 x 0.8 (0.2)] / 0.0475 x 0.0475 = 64

Hence sample size of 66 children were selected for the study.

Inclusion criteria

- All patients diagnosed as chronic kidney disease in accordance with KDOQI guidelines having less than 18 years of age

Exclusion criteria:

- Patients who have pre-existing hypothyroidism/ hyperthyroidism.
- CKD patients on drugs which are known to affect thyroid function like interferon etc.
- CKD child in acute decompensation.

METHODOLOGY

The study was done at our tertiary care centre on all CKD childrenin the department of Pediatrics, OPD of BJWCH on attending OPD/IPD after due permission from the Institutional Ethics Committee and Review Board and after taking Written Informed Consent from the patients.

After approval from the Institutional Ethics Committee a valid informed consent was taken. Once the patients were enrolled for the study, a thorough history and physical examination was done as per proforma. An informed consent was taken in written from patients or patient's attendant.

It is a single centre prospective observational study. Study was done at our tertiary care centre on patients coming for the follow up in CKD OPD of BJWCH and newly diagnosed CKD children admitted in ward or coming in the OPD after metabolic stabilization. Patients fulfilling the inclusion criteria were enrolled in the study after taking parental informed consent or assent.

A study proforma was made which focused on demographic features, caste, residence location, source of water, kind of salt consumed, family history of hypothyroidism, age at the diagnosis of CKD, clinical features and baseline laboratory tests, different stages of CKD.

Additionally history, examination was done to look for clinical features of hypothyroidism-history, thyroid swelling. All recruited patients had undergone examination to look for of serum Free T3, T4, TSH at the time of enrollment.

These all investigations are routinely done in chronic kidney disease patient coming to OPD for follow up.
BUN- Cl
Creatinine- pH
Egfr- pCO2
Calcium- HCO3
Phosphrus Free - T3
Alkaline phosphate Free - T4
Na+ - TSH
K+ - Serum Albumin
Urine routine microscopy- 24hrs urine albumin

RESULTS AND DISCUSSION:

A hospital based prospective observational study was conducted with 66 children to assess the prevalence of abnormal thyroid functions in children with chronic kidney disease and to correlate abnormal thyroid functions with different etiologies of chronic kidney disease and different stages of chronic kidney disease.

Distribution of children as per Thyroid Function Test Results

28 out of 66 children had thyroid disorders. The prevalence of thyroid disorders in our study was 42.4%. The prevalence of subclinical hypothyroidism and hypothyroidism was 33.3% and 9.1% respectively.

Table: Distribution of children as per Thyroid Function Test Results

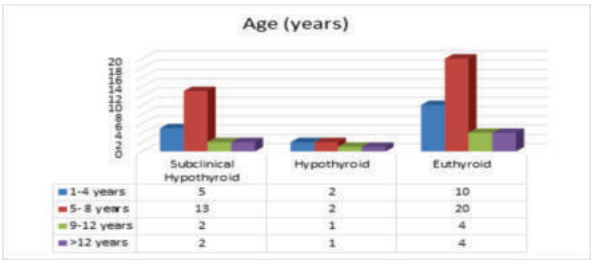
Thyroid Status	N	%
Subclinical Hypothyroidism	22	33.3%
Hypothyroidism	6	9.1%
Euthyroid	38	57.6%
Total	66	100%

Distribution of children according to Age

The mean age of children with subclinical hypothyroid and hypothyroid was 6.95 ± 2.94 years and 6.83 ± 3.82 years respectively while the mean age of euthyroid children was 6.97 ± 3.21 years. There was no significant difference between the groups as per ANOVA test (p>0.05)

Table 1: Distribution of children according to Age

Age (years)	Subclinical Hypothyroid		Hypothyroid		Euthyroid		p Value
	N	%	N	%	N	%	
1-4 years	5	22.7%	2	33.3%	10	26.3%	>0.05
5- 8 years	13	59.1%	2	33.3%	20	52.7%	
9-12 years	2	9.1%	1	16.7%	4	10.5%	
>12 years	2	9.1%	1	16.7%	4	10.5%	
Total	22	100%	6	100%	38	100%	
Mean ± SD	6.95 ± 2.94		6.83 ± 3.82		6.97 ± 3.21		



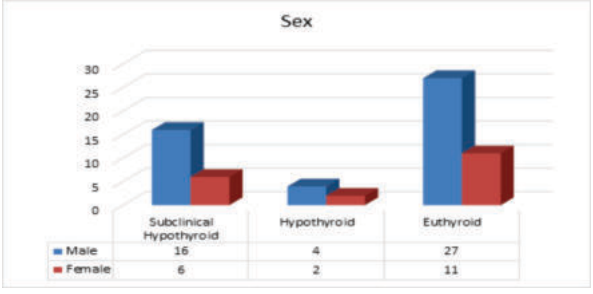
Graph 1: Distribution of children according to Age

Distribution of children according to Sex

16 (72.7%) and 6 (27.3%) children with subclinical hypothyroid were male and female respectively while 4 (66.7%) and 2 (33.3%) children with hypothyroid were male and female respectively. 27 (71.1%) and 11 (28.9%) euthyroid children were male and female respectively. There was no significant difference between the groups as per Chi-Square test (p>0.05).

Table 2: Distribution of children according to Sex

Sex	Subclinical Hypothyroid		Hypothyroid		Euthyroid		p Value
	N	%	N	%	N	%	
Male	16	72.7%	4	66.7%	27	71.1%	>0.05
Female	6	27.3%	2	33.3%	11	28.9%	
Total	22	100%	6	100%	38	100%	



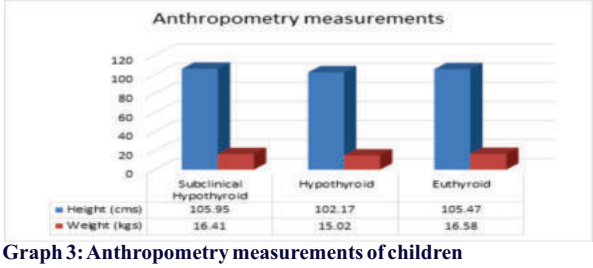
Graph 2: Distribution of children according to Sex

Anthropometry measurements of children

The mean height of children with subclinical hypothyroid and hypothyroid was 105.95 ± 15.19 cms and 102.17 ± 24.01 cms respectively while the mean height of euthyroid children was 105.47 ± 16.28 cms. The mean weight of children with subclinical hypothyroid and hypothyroid was 16.41 ± 6.27 kgs and 15.02 ± 6.29 kgs respectively while the mean weight of euthyroid children was 16.58 ± 6.59 kgs. There was no significant difference between the groups as per ANOVA test (p>0.05).

Table 3: Anthropometry measurements of children

Anthropometry measurements	Subclinical Hypothyroid		Hypothyroid		Euthyroid		p Value
	Mean	SD	Mean	SD	Mean	SD	
Height (cms)	105.95	15.19	102.17	24.01	105.47	16.28	>0.05
Weight (kgs)	16.41	6.27	15.02	6.29	16.58	6.59	



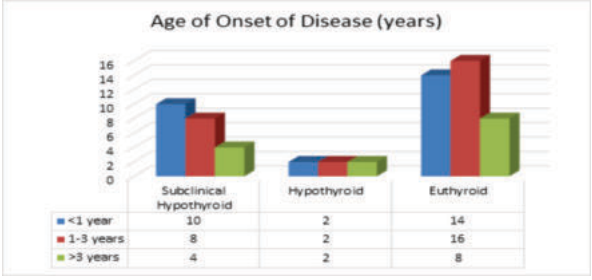
Graph 3: Anthropometry measurements of children

Distribution of children according to Age of Onset of Disease

The mean age of onset of disease of children with subclinical hypothyroid and hypothyroid was 3.71 ± 2.5 years and 4.38 ± 3.90 years respectively while the mean age of onset of disease of euthyroid children was 3.69 ± 2.55 years. There was no significant difference between the groups as per ANOVA test (p>0.05).

Table 4: Distribution of children according to Age of Onset of Disease

Age of Onset of Disease (years)	Subclinical Hypothyroid		Hypothyroid		Euthyroid		p Value
	N	%	N	%	N	%	
<1 year	10	45.4%	2	33.3%	14	36.7%	>0.05
1-3 years	8	36.4%	2	33.3%	16	42.2%	
>3 years	4	18.2%	2	33.3%	8	21.1%	
Total	22	100%	6	100%	38	100%	
Mean ± SD	3.71 ± 2.58		4.38 ± 3.90		3.69 ± 2.55		



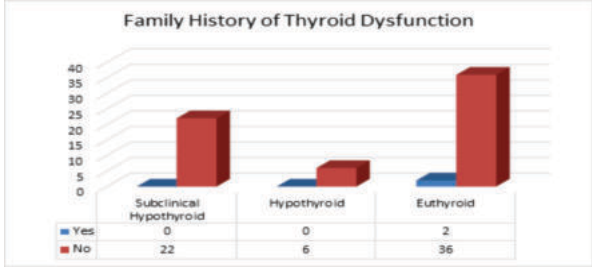
Graph 4: Distribution of children according to Age of Onset of Disease

Distribution of children according to Family History of Thyroid Dysfunction

No child with subclinical hypothyroid and hypothyroid had family history of thyroid dysfunction while 2 (5.3%) euthyroid children had family history of thyroid dysfunction. There was no significant difference between the groups as per Chi-Square test (p>0.05).

Table 5: Distribution of children according to Family History of Thyroid Dysfunction

Family History of Thyroid Dysfunction	Subclinical Hypothyroid		Hypothyroid		Euthyroid		p Value
	N	%	N	%	N	%	
Yes	0	-	0	-	2	5.3%	>0.05
No	22	100%	6	100%	36	94.7%	
Total	22	100%	6	100%	38	100%	



Graph 5: Distribution of children according to Family History of Thyroid Dysfunction

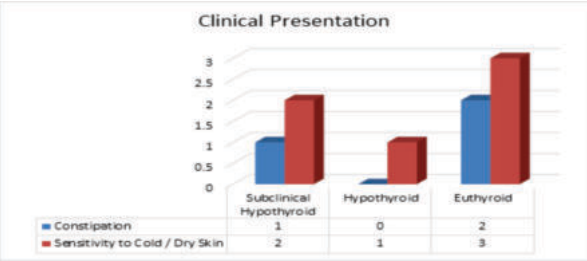
Distribution of children according to Clinical Presentation

1 (4.5%) and 2 (9.1%) children with subclinical hypothyroid had constipation and sensitivity to cold / dry skin respectively while 1 (16.7%) child with hypothyroid had sensitivity to cold / dry skin. 2 (5.3%) and 3 (7.9%) euthyroid children had constipation and sensitivity to cold / dry skin respectively. There was no significant difference between the groups as per Chi-Square test (p>0.05).

Table 6: Distribution of children according to Clinical Presentation

Clinical Presentation	Subclinical Hypothyroid		Hypothyroid		Euthyroid		p Value
	N	%	N	%	N	%	

Constipation	1	4.5%	0	-	2	5.3%	>0.05
Sensitivity to Cold / Dry Skin	2	9.1%	1	16.7%	3	7.9%	



Graph 6: Distribution of children according to Clinical Presentation

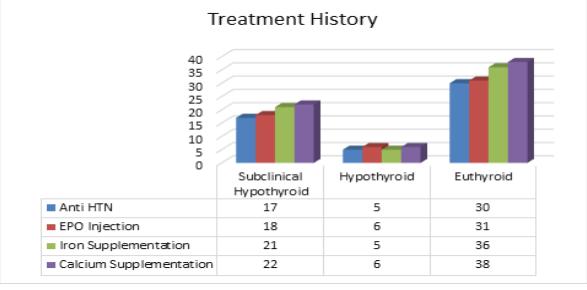
Distribution of children according to Treatment History

17 (77.3%) and 18 (81.8%) children with subclinical hypothyroid were prescribed anti HTN and EPO injection respectively while 21 (95.4%) and 22 (100%) children were on iron and calcium supplementation respectively. 5 (83.3%) and 6 (100%) children with hypothyroid were prescribed anti HTN and EPO injection respectively while 5 (83.3%) and 6 (100%) children were on iron and calcium supplementation respectively.

30 (78.9%) and 31 (81.6%) euthyroid children were prescribed anti HTN and EPO injection respectively while 36 (94.7%) and 38 (100%) children were on iron and calcium supplementation respectively. There was no significant difference between the groups as per Chi-Square test (p>0.05).

Table 7: Distribution of chidren according to Treatment History

Treatment History	Subclinical Hypothyroid		Hypothyroid		Euthyroid		p Value
	N	%	N	%	N	%	
Anti HTN	17	77.3%	5	83.3%	30	78.9%	>0.05
EPO Injection	18	81.8%	6	100%	31	81.6%	
Iron Supplementation	21	95.4%	5	83.3%	36	94.7%	
Calcium Supplementation	22	100%	6	100%	38	100%	



Graph 7: Distribution of children according to Treatment History

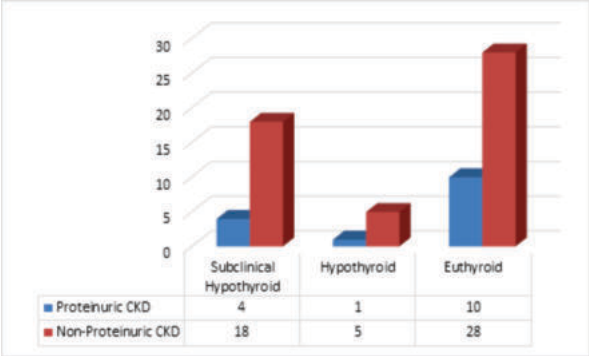
Distribution of children according to Proteinuric CKD

4 (18.2%) and 1 (16.7%) child with subclinical hypothyroid and hypothyroid respectively had proteinuric CKD while 10 (26.3%) euthyroid children had proteinuric CKD. There was no significant difference between the groups as per Chi-Square test (p>0.05).

Table 8: Distribution of children according to Proteinuric CKD

	Subclinical Hypothyroid		Hypothyroid		Euthyroid		p Value
	N	%	N	%	N	%	
Proteinuric CKD	4	18.2%	1	16.7%	10	26.3%	>0.05
Non-Proteinuric CKD	18	81.8%	5	83.3%	28	73.7%	
Total	22	100%	6	100%	38	100%	

Graph 8: Distribution of children according to Proteinuric CKD



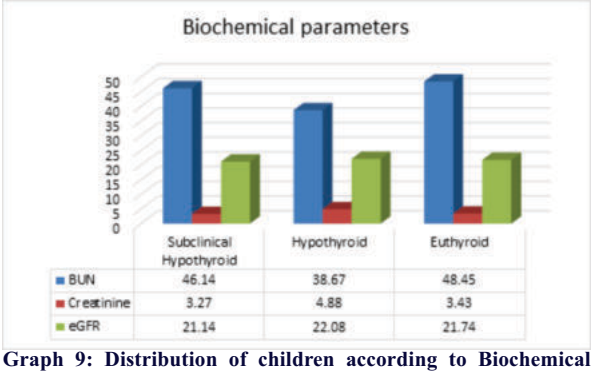
Distribution of children according to Biochemical parameters

The mean BUN, creatinine and eGFR values of children with subclinical hypothyroid were 46.14±18.53mg/dL, 3.27±2.27mg/dL and 21.14±12.19 ml/min/1.73m^2 respectively. The mean BUN, creatinine and eGFR values of children with hypothyroid were 38.67±15.54mg/dL, 4.88±1.92mg/dL and 22.08±21.05 ml/min/1.73m^2 respectively.

The mean BUN, creatinine and eGFR values of euthyroid children were 48.45±19.81mg/dL, 3.43±2.46mg/dL and 21.74±12.46 ml/min/1.73m^2 respectively. There was no significant difference between the groups as per Chi-Square test (p>0.05).

Table 9: Distribution of childrn according to Biochemical parameters

Biochemical parameters	Subclinical Hypothyroid		Hypothyroid		Euthyroid		p Value
	Mean	SD	Mean	SD	Mean	SD	
BUN	46.14	18.53	38.67	15.54	48.45	19.81	>0.05
Creatinine	3.27	2.27	4.88	1.92	3.43	2.46	
eGFR	21.14	12.19	22.08	21.05	21.74	12.46	



Graph 9: Distribution of children according to Biochemical parameters

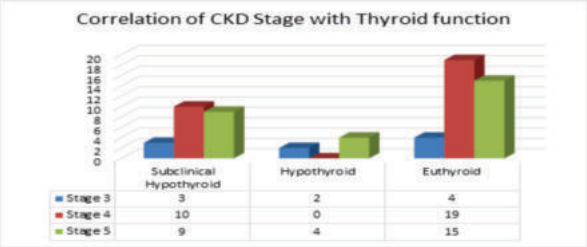
Correlation of CKD Stage with Thyroid function of children

3 (13.6%) and 10 (45.5%) children with subclinical hypothyroid had Stage 3 and Stage 4 CKD respectively while 9 (40.9%) children had Stage 5 CKD. 2 (33.3%) and 4 (66.7%) children with hypothyroid had Stage 3 and Stage 5 CKD respectively.

4 (10.5%) and 19 (50%) euthyroid children had Stage 3 and Stage 4 CKD respectively while 15 (39.5%) children had Stage 5 CKD. It was observed that with increasing severity of CKD, hypothyroidism also increase from 33.3% in stage 3 to 66.7% in stage 5 CKD. There was correlation of CKD Stage with thyroid function of children as per Chi-Square test (p<0.05).

Table 10: Correlation of CKD Stage with Thyroid function of children

CKD Stage	Subclinical Hypothyroid		Hypothyroid		Euthyroid		p Value
	N	%	N	%	N	%	
Stage 3	3	13.6%	2	33.3%	4	10.5%	<0.05
Stage 4	10	45.5%	0	-	19	50%	
Stage 5	9	40.9%	4	66.7%	15	39.5%	
Total	22	100%	6	100%	38	100%	



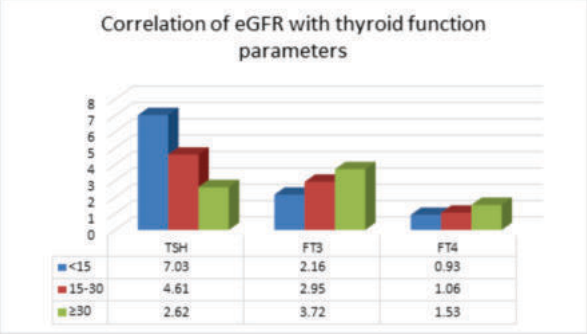
Graph 10: Correlation of CKD Stage with Thyroid function of children

Correlation of eGFR with thyroid function parameters

It was observed that with decrease in eGFR values there was significant increase in TSH values and significant decrease in FT3 values while the difference in FT4 value was comparable. There was significant correlation of eGFR with TSH and FT3 values as per ANOVA test ($p<0.05$).

Table 11: Correlation of eGFR with thyroid function parameters

eGFR (ml/min/1.73m2)	TSH		Ft3		Ft4	
	Mean	SD	Mean	SD	Mean	SD
<15	7.03	4.64	2.16	0.75	0.93	0.22
15-30	4.61	2.07	2.95	0.42	1.06	0.25
≥30	2.62	1.78	3.72	0.97	1.53	0.39
p Value	<0.05		<0.05		>0.05	



Graph 11: Correlation of eGFR with thyroid function parameters

A hospital based prospective observational study was conducted with 66 children to assess the prevalence of abnormal thyroid functions in children with chronic kidney disease and to correlate abnormal thyroid functions with different etiologies of chronic kidney disease and different stages of chronic kidney disease.

The interplay between thyroid and the kidney in each other's functions is known for many years. Thyroid dysfunction affects renal physiology and development, whereas kidney disease could result in thyroid dysfunction. Disorders of the thyroid and kidney may co-exist with common etiological factors. In addition, treatment strategies of one disease may affect those of the other organ.

There are several interactions between thyroid and kidney functions in each other organ's disease states. Thyroid hormones affect renal development and physiology. Thyroid hormones have pre-renal and intrinsic renal effects by which they increase the renal blood flow and the glomerular filtration rate (GFR). Hypothyroidism is associated with reduced GFR and hyperthyroidism results in increased GFR as well as increased renin – angiotensin – aldosterone activation. CKD patients also have increased incidence of primary hypothyroidism and subclinical hypothyroidism.

In the present study, 28 out of 66 children had thyroid disorders. The prevalence of thyroid disorders in our study was 42.4%. The prevalence of subclinical hypothyroidism and hypothyroidism was 33.3% and 9.1% respectively. This is similar to the studies of El-Hana NA et al[19] and Bajaj S et al[20]. El-Hana NA et al[19] found out of the total number of patients, 36 (72%) had normal thyroid function, and dysfunctional thyroid incidence affecting children with CRF was 28% (14 patients) Nine (64.2%) were diagnosed with subclinical hypothyroidism, three (21.4%) with ESS and two (14.2%) with primary hypothyroidism.

Bajaj S et al[20] prospective study assessing the Prevalence of hypothyroidism in nondiabetic CKD found among all cases, 32 (43.8%) were hypothyroid, 30 (41.1%) had SCH and 2 (2.7%) patients had OH. Prevalence of hypothyroidism increased with increasing severity of CKD. There were 1 (3.1%) case with hypothyroidism in stage 3b, 8 (25%) cases in stage 4 and 23 (71.9%) cases in stage 5

Conclusion:There are various mechanisms of interaction between kidney and thyroid functions in the disease states of each other organ. Thyroid dysfunction is very common in CKD patients and reveals the significant association between CKD progression and thyroid dysfunction and mean of T3, T4 decreases and TSH increases significantly in CKD. A decrease in eGFR values was significant increase in TSH values and significant decrease in FT3 values while the difference in FT4 value was comparable. There was significant correlation of eGFR with TSH and FT3 values.Health professionals caring for patients with CKD should be cognizant that CKD and hypothyroidism may exhibit overlapping symptom complexes. Hyperthyroidism which was found in some previous studies was not found in this study.

REFERENCES:

1. Kaptein EM. Thyroid function in renal failure. Contrib Nephrol. 1986;50:64–72.
2. Ramírez G, Jubiz W, Gutch CF et al. Thyroid abnormalities in renal failure. A study of 53 patients on chronic hemodialysis. Ann Intern Med. 1973;79:500.
3. Kaptein EM. Thyroid hormone metabolism and thyroid diseases in chronic renal failure. Endocr Rev. 1996;17:454-63.
4. Dallas JS and Foley TP Jr, Hypothyroidism In: Paed Endocrinology by Fima Lifshitz, 2006:469-481.
5. Lo JC, Chertow GM, Go AS ET AL. Increased prevalence of subclinical and clinical hypothyroidism in persons with chronic kidney disease. Kidney international. 2005;67:10474–1052.
6. Chonchol M, Lippi G, Salvagno G et al. Prevalence of subclinical hypothyroidism in patients with chronic kidney disease. Clinical journal of the American Society of Nephrology: CJASN. 2008;3:12964–1300.
7. Wijkhuisen A, Djouadi F, Vilar J et al. Thyroid hormones regulate development of energy metabolism enzymes in rat proximal convoluted tubule. Am J Physiol. 1995;268:F634–42
8. Den Hollander JG, Wulkan RW, Mantel MJ et al. Correlation between severity of thyroid dysfunction and renal function. Clin Endocrinol (Oxf). 2005; 62:423–7.
9. Kobori H, Ichihara A, Miyashita Y et al. Mechanism of hyperthyroidism-induced renal hypertrophy in rats. J Endocrinol. 1998;159:9–14.
10. Kimmel M, Braun N, Alscher M. Influence of thyroid function on different kidney function tests. Kidney Blood Press Res. 2012;35:9–17.
11. Suher M, Koc E, Ata N et al. Relation of thyroid disfunction, thyroid autoantibodies, and renal function. Ren Fail. 2005;27:739–42.
12. Van Welsem ME, Lobatto S. Treatment of severe hypothyroidism in a patient with progressive renal failure leads to significant improvement of renal function. Clin Nephrol. 2007;67:391–3.
13. Mariani LH, Berns JS. The renal manifestations of thyroid disease. Journal of the American Society of Nephrology: JASN. 2012; 23:224–26.
14. Kreisman SH, Hennessey JV. Consistent reversible elevations of serum creatinine levels in severe hypothyroidism. Archives of internal medicine. 1999;159:794–82.
15. Villabona C, Sahun M, Roca M et al. Blood volumes and renal function in overt and subclinical primary hypothyroidism. The American journal of the medical sciences. 1999;318:2774–280.
16. Rhee CM, Bhan I, Alexander EK et al. Association between iodinated contrast media exposure and incident hyperthyroidism and hypothyroidism. Archives of internal medicine. 2012;172:1534–159.
17. Silverberg DS, Ulan RA, Fawcett DM et al. Effects of chronic hemodialysis on thyroid function in chronic renal failure. Can Med Assoc J. 1973; 109:282–6.
18. Kaptein EM, Levenson H, Siegel ME et al. Radioiodine dosimetry in patients with end-stage renal disease receiving continuous ambulatory peritoneal dialysis therapy. J Clin Endocrinol Metab. 2000;85:3058–64.
19. El-Hana NA, El Shaikh S, Shaheen FA. Thyroid Function in Children with Chronic Renal Failure. Saudi J Kidney Dis Transpl. 1996; 7:297-300.
20. Bajaj S, Purwar N, Gupta A et al. Prevalence of hypothyroidism in nondiabetic chronic kidney disease and effect of thyroxine replacement on estimated glomerular filtration rate. Indian J Nephrol. 2017;27:104-7.
21. Punekar J, Singh AA, Malav MK. Study of thyroid function in patients with chronic kidney disease. Int J Health Sci Res. 2017;7(2):68-72.
22. Gupta UN, Jain A, Prakash P etal. To study the prevalence of thyroid disorders in chronic renal disease patients. J Integr Nephrol Androl. 2018;5:126-9.