Prospective study of thyroid functions in children with chronic kidney disease

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Research Article

Keywords: subclinical hypothyroidism, chronic kidney disease

Posted Date: July 1st, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1761891/v1

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. 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. It has been shown that in CKD, as the GFR falls there is a higher possibility of developing clinical and subclinical hypothyroidism.

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.

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 OPD/IPD.

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:

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

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.

The study was done at our tertiary care centre on all CKD children in 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 & graph 1).

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 & graph 2).

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 & graph 3).

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 & graph 4).

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 & graph 5).

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 & graph 6).

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 & graph 7).

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 & graph 8).

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 & graph 9).

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 & graph 10).

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 & graph 11).

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 & graph 12).

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].

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.

Declarations

Funding: Patients have paid for the tests.

Authors' contributions: Dr.Qudsiya Ansari has done this study under Dr.Alpana Ohri’s guidance.

Ethics approval: Ethics approval has be taken from Institutional Ethics committee of KEM hospital before starting the study.

Consent to participate: informed consent has been taken from patients for the study and publication.

Conflicts of interest/Competing interests: not applicable

Availability of data and material: all data reports collected during study is available with author.

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Tables

Table 1: 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%

Table 2: 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		

Table 3: 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%	

Table 4: 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	

Table 5: 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		

Table 6: 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%	

Table 7: 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%	

Table 8: Distribution of children 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%	

Table 9: 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%	

Table 10: Distribution of children 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	

Table 11: 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%	

Table 12: Correlation of eGFR with thyroid function parameters

eGFR (ml/min/1.73m^2)	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	

Graphs

Graph 1 to 12 is available in Supplementary Files section.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Graph.docx