Thyroid Profile in Pediatric Patients with Chronic Kidney Disease

Thesis

Submitted for Partial Fulfillment of
MS Degree in ***Pediatrics***

By

Dina Ashraf El-Agouze
M.B,B.Ch
Faculty of Medicine – Ain Shams University

Supervised By

Prof. Dr. Ihab Zaki El-Hakim
Professor of Pediatrics
Faculty of Medicine - Ain Shams University

Prof. Dr. Mona Rashad Aly
Professor of Pediatrics
Faculty of Medicine - Ain Shams University

Dr. Dina Aly Mohamed
Lecturer of Clinical Pathology
Faculty of Medicine – Ain Shams University

Faculty of Medicine
Ain Shams University
2018

سورة البقرة الآية: ٣٢

Acknowledgments

First and foremost, I feel always indebted to ***Allah*** *the Most Beneficent and Merciful.*

I would like to thank my dear professors, Prof. ***Dr. Ihab Zaki El-Hakim****, Professor of pediatrics Ain Shams University, and* ***Prof. Dr. Mona Rashad Ali****, Professor of pediatrics Ain Shams University, for their great support and guidance throughout this thesis.*

I would like also to thanks ***Dr. Dina Ali****, lecturer of clinical pathology Ain Shams University, for her great help in this study.*

Finally, my deepest gratitude goes to ***my family*** *for their un-flagging love and unconditioned support throughout my life.*

I thank all who in one way or another contributed in the completion of this thesis.

Dina Ashraf El-Agouze

List of Contents

List of Tables

List of Figures

List of Abbreviations

Abb.	Full term
ACTH	*Adrenocorticotrophic Hormone*
CAKUT	*Congenital Anomalies Of The kidney And Urinary Tract.*
CKD	*Chronic Kidney Disease*
DIT	*Diiodotyrosine*
eGFR	*Estimated Glomerular Filtration Rate*
ESKD	*End Stage Kidney Disease*
FT3	*Free Tri-iodothyronine*
FT4	*Free Tetra-iodothyronine*
GBM	*Glomerular Basement Membrane*
GFR	*Glomerular Filtration Rate*
HD	*Hemodialysis*
MIT	*Monoiodotyrosine*
NKF-K/DOQ	*National Kidney Foundation's Kidney Disease Outcomes Quality Initiative*
NO	*Nitric Oxide*
NOS	*Nitric Oxide Synthase*
PD	*Peritoneal dialysis*
RRT	*Renal Replacement Therapy*
rT3	*Reverse Triiodothyronine*
SD	*Standard deviation*
TBPA	*Thyroid Binding Pre-Albumin*
TRH	*Thyrotropin-Releasing Hormone*
TSH	*Thyroid-Stimulating Hormone*

INTRODUCTION

The kidney plays an important role in the metabolism, degradation, and excretion of thyroid and hypothalamic-pituitary-thyroid axis hormones (TSH and TRH). It is not surprising, therefore, that impairment in kidney function leads to disturbed thyroid physiology. Normal renal function is influenced by the biologically active thyroid hormone T3. Kidney tissue possesses a thyroxine-5'-deiodinase, which converts thyroxin (T4) to triiodothyronine (T3) ***(Oppenheimer, 1990 & Kaptein, 1996).*** Patients with chronic kidney disease (CKD) have normal total serum reverse T3 (rT3) levels rather than the elevated values observed in most non-renal non-thyroidal disorders ***(Kaptein, 1986 & Shamsadini et al., 2006).*** In chronic kidney disease (CKD), normal serum total rT3 level is observed and associated with elevated free rT3 concentrations due to reduced free rT3 clearance rate ***(Kaptein et al., 1983).***

CKD affects both hypothalamus–pituitary–thyroid axis and thyroid hormones (T3 and T4) peripheral metabolism ***(Singh et al., 2013).***

Epidemiological studies indicate that the incidence of primary thyroid disorders, is slightly higher in patients with CKD than in the general population, with higher prevalence of primary hypothyroidism, both overt and subclinical, but not with hyperthyroidism ***(Chonchol et al., 2008).***

Prevalence of hyperthyroidism in CKD population does not vary from the general population ***(Kaptein el al., 2004).*** However, few cases were reported in the medical literature ***(Nibhanupudy et al., 1993).***

Hyperthyroidism can accelerate chronic kidney disease (CKD) by several mechanisms: (i)Increased renal blood flow seen in hyperthyroidism results in intra-glomerular hypertension, leading to increased filtration pressure and consequent hyper-filtration which causes proteinuria, causing direct renal injury ***(Van Hoek & Daminet, 2009)*** (ii)Increased mitochondrial energy metabolism along with downregulation of superoxide dismutase, contributes to an increased free radical generation that causes renal injury ***(Vargas et al., 2006).*** (iii) Oxidative stress also contributes to hypertension in hyperthyroidism, which contributes to CKD progression ***(Basu & Mohapatra, 2012).***

Hypothyroidism can accelerate chronic kidney disease (CKD) by several mechanisms: (i) Hypothyroidism decreases cardiac output which in turn decreases renal blood flow. (ii)It causes pathological changes in glomerular structure e.g. glomerular basement membrane thickening and mesangial matrix expression which reduces renal blood flow. (iii)It decreases GFR.

Despite the negative impact of hypothyroidism on GFR, some investigators reported that hypothyroidism could be described as rather beneficial for the progression of CKD ***(Conger et al., 1989)***.

Aim of the Work

To study thyroid dysfunction in pediatric patients with CKD.

CHRONIC KIDNEY DISEASE

Chronic kidney disease (CKD) is a major health worldwide problem with increase in its incidence, that is threatening to be a real epidemic problem and it is often described as the "silent killer" in medicine, as the disease is not often symptomatic until the glomerular filtration rate (GFR) is severely decreased ***(Brück et al., 2015).***

CKD is a gradual loss of kidney function over time. The definition of CKD is developed by time, so currently the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines have defined CKD as abnormalities of kidney structure or function (abnormal urine analysis, imaging study) with or without decline in GFR, or decline in glomerular filtration rate (GFR) below 60 mL/min/1.73 m^2 of body surface area or both of at least 3 months duration ***(KDIGO clinical practice, 2013).***

For children below 2 years of age, it is recommended by The National Kidney Foundation to closely monitor children with values of GFR below the mean by more than 1 standard deviation, as the criteria for duration >3 months in not applicable on newborns or infants <3 months of age and the criteria of a GFR <60 ml/min/1.73 m^2 is not applicable to children <2 years of age as neonates are born with a GFR of around 60 ml/min/1.73 m^2, and increases to normal values in the first 2 years of life ***(Schwartz et al., 2009).***

Unfortunately, the term CKD defines renal dysfunction as progressive, rather than discrete change in renal function ***(KDIGO clinical practice 2012).***

Staging of CKD:

In 2002, the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI) classified CKD to five stages, independent of cause, but based on the level of GFR. This classification was revised in 2013(table1) ***(KDIGO clinical practice guideline 2013).***

Table (1): K/DOQI stages of chronic kidney disease.

Stage	Description	Glomerular filtration rate
Stage 1	Kidney damage with normal GFR	>90ml/min/ 1.73 m^2
Stage 2	Kidney damage with mild decrease in GFR	60-89ml/min/ 1.73 m^2
Stage 3a Stage 3b	Mild decrease in GFR	45-59ml/min/ 1.73 m^2 30-44ml/min/ 1.73 m^2
Stage 4	Sever decrease in GFR	15-29ml/min/ 1.73 m^2
Stage 5	Kidney failure	<15ml/min/ 1.73 m^2

Kidney Disease: Improving Global outcomes ***(KDIGO, 2012).***

Epidemiology of CKD:

In adult patients with CKD and ESKD, there have been extensive epidemiological research, but fewer data are available about CKD and ESKD in children ***(Harambat et al., 2012).***

Epidemiology of CKD may be underestimated as CKD is often clinically asymptomatic, especially in earlier stages ***(Wong & Warady, 2016).***

Despite the underestimation, the pediatric incidence of CKD in Europe is reported to be around 11–12 per million of age-related population for stages 3–5 ***(ESPN, 2016).***

The incidence of CKD in children in developing countries is not well clarified, especially in those countries where the healthcare resource to renal replacement therapy (RRT) is inadequate or not available, and most children affected by CKD die ***(Warady & Chadha, 2007).***

Higher values for incidence has been reported in the USA, probably because renal replacement therapy (RRT) is started earlier, at higher levels of GFR, in comparison with other developed countries ***(Saran et al., 2017).***

In Egypt, because of limited diagnostic resources and poor-quality primary health care, ESRD is probably the "tip of the iceberg," where patients are diagnosed with renal disease when they have already reached the end-stage renal failure ***(Safouh et al., 2015).***

According to gender, the incidence of CKD is greater in males than females because of the higher frequency of congenital abnormalities of the kidney and urinary tract (CAKUT) in males ***(Harambat et al., 2012).***

Etiology of CKD:

According to pediatric epidemiologic studies, CKD may due to congenital, acquired, inherited or metabolic renal diseases. Etiologies of CKD can be divided into two categories; glomerular and non-glomerular causes ***(Furth et al., 2011).***

The main etiologic factors of CKD in children are congenital anomalies of the kidney and urinary tract (CAKUT). The most common causes in this category are; obstructive uropathy, aplastic/hypo-plastic/polycystic kidney, and reflux nephropathy (table2).***(Vivante & Hildebrandt, 2016).***

Table (2): Etiology of CKD in pediatrics.

Glomerular causes:	Non-Glomerular causes:
Hemolytic uremic syndrome	Obstructive uropathy
Systemic immunological disease (eg. SLE)	Congenital anomalies (aplastic/hypoplasic/polycystic kidney)
Familial nephritis	Reflux nephropathy
IgA nephropathy	Pyelonephritis
Henoch-Scholein pupura	Metabolic disorder (eg. Oxalosis, cystinosis)
Congenital nephrotic syndrome	Wilms' tumor
Focal and segmental glomerulonephritis	Renal vein thrombosis

(Furth et al., 2011)

In Egypt, a study was conducted in 2015 and published about the etiology of CKD among the Egyptian pediatric CKD patients, showed that the most common cause of CKD was obstructive uropathy, followed by primary glomerulonephritis, reflux nephropathy, aplasia/hypoplasia and familial/metabolic diseases ***(Safouh et al., 2015).***

Clinical presentation and pathophysiology:

Many patients are discovered accidentally during routine medical examination in the early stage of CKD as they are mostly asymptomatic, or when they are symptomatic but after they became with advanced CKD ***(Ishani et al., 2006).***

Table (3): Clinical presentation and pathophysiology of CKD:

Presentation:	Pathophysiology:
• Anemia	• Uremia-induced inhibitors of erythropoiesis. • Shortened red blood cell survival. • Iron deficiency (impairing dietary absorption, dietary iron deficiency, gastrointestinal loss). • Chronic inflammation(Complement activation from dialysis, Systemic inflammatory diseases as in SLE). • Bone marrow suppression (Inhibitory factors, hyperparathyroidism, immunosuppressive drugs) • Increased red cell turnover. • Malnutrition B12 or folate deficiency.
• Cvs	• <u>Cardiac affection:</u> 1. Left ventricular hypertrophy (due to hypertension, anemia and volume overload). 2. Hypertension (due to volume overload and excessive renin production). 3. Arrhythmia(due to electrolyte disturbance)