بسم الله الرحمن الرحيم

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تم رفع هذه الرسالة بواسطة / حسام الدين محمد مغربي

بقسم التوثيق الإلكتروني بمركز الشبكات وتكنولوجيا المعلومات دون أدنى مسئولية عن محتوى هذه الرسالة.

ملاحظات : لا يوجد

Hyperinsulinemia and Insulin Resistance in Pediatric Patients with Chronic Kidney Disease

Thesis

Submitted for Partial Fulfillment of Master's Degree in Pediatrics

By

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2022

سورة البقرة الآية: ٣٢

Acknowledgment

First and foremost, I feel always indebted to **ALLAH,**
the Most Kind and Most Merciful.

I'd like to express my respectful thanks and profound gratitude to **Prof. Dr. Hamed Ahmed El-Khayat,** *Professor of Pediatrics, Faculty of Medicine, Ain Shams University for his keen guidance, kind supervision, valuable advice and continuous encouragement, which made possible the completion of this work.*

I am also delighted to express my deepest gratitude and thanks to **Dr. Dina Ebrahem Darweish Sallam,** *Lecturer of Pediatrics, Faculty of Medicine, Ain Shams University, for her kind care, continuous supervision, valuable instructions, constant help and great assistance throughout this work.*

I am deeply thankful to **Dr. Marwa Ali Abdel Wahed Ali,** *Lecturer of Clinical Pathology, Faculty of Medicine, Ain Shams University, for her great help, active participation and guidance.*

I wish to introduce my deep respect and thanks to **Dr. Ahmed Ashraf Mahmoud Okba,** *Lecturer of Diagnostic and Interventional Radiology, Faculty of Medicine, Ain Shams University, for his kindness, supervision and cooperation in this work.*

I wish to express my deepest thanks, gratitude and appreciation to **Dr. Samer Hamed El-Khayat,** *Lecturer of Pediatrics, Faculty of Medicine, Ain Shams University for his meticulous supervision, kind guidance, valuable instructions and generous help.*

Special thanks are due to **Dr. Yasmine El Henawy,** *for her sincere efforts and fruitful encouragement.*

Rawan Ahmed

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List of Abbreviations

Abb.	Full term
ABPM	Ambulatory BP monitoring
ACR	Albumin/creatinine ratio
AER	Albumin excretion rate
BBB	Blood–brain barrier
BMI	Body mass index
BP	Blood pressure
BSA	Body surface area
Ca	Calcium
CAKUT	Congenital anomalies of the kidney and urinary tract
CCA	Common carotid artery
CKD	Chronic kidney disease
CKiD	Chronic Kidney Disease in Children
CVD	Cardiovascular disease
ED	Endothelial dysfunction
EF%	Ejection fraction %
ER	Endoplasmic reticulum
ESCAPE	Effect of Strict Blood Pressure Control and Angiotensin Converting Enzyme Inhibition on the Progression of Chronic Renal Failure in Pediatric Patients
ESKD	End-stage kidney disease
GFR	Glomerular filtration rate
GH	Growth hormone
GN	Chronic glomerulonephritis, nephritis
HD	Hemodialysis
HDL	High density lipoproteins
Hgb%	Haemoglobin %
HOMA-IR	Homeostasis model assessment for insulin resistance
HRQOL	Health-related quality of life

List of Abbreviations Cont...

Abb.	Full term
HT	Hypertension
ICA	Internal carotid artery
IGF-I	Insulin-like growth factor-I
IL	Interleukin
IR	Insulin resistance
IRB	Institutional Review Board
KDIGO	Kidney Disease: Improving Global Outcomes
LDL	Low-density lipoprotein
LV	Left ventricular
MAP	Mean arterial blood pressure
NAPRTCS	North American Pediatric Renal Collaborative Trials
NO	Nitric oxide
OGTT	Oral glucose tolerance test
PO4	Phosphorus
QOL	Quality of life
QUICKI	Quantitative insulin sensitivity check index
RAAS-I	Renin-angiotensin-aldosterone system inhibitors
ROS	Reactive Oxygen Species
sHPT	Secondary hyperparathyroidism
sICAM	Soluble intercellular adhesion molecule
SLE	Systemic lupus erythematosus
SRNS	Steroid-resistant nephrotic syndrome
sUA	Serum uric acid
sVCAM	Soluble vascular cell adhesion molecule
TIN	Chronic tubulointerstitial
TMA	Thrombotic Microangiopathy
TNF	Tumor necrosis factor
UPR	Unfolded protein response
VEGF	Vascular endothelial growth factor

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Abstract:

Background: Pediatric chronic kidney disease (CKD) is associated with disturbance of glucose metabolism & insulin receptor sensitivity leading to impaired glucose tolerance & insulin resistance (IR), which are potential risk factors for cardiovascular disease (CVD). Hyperinsulinemia and IR are not extensively investigated in children with CKD, especially in different stages of CKD. **Subjects & methods:** A total of 87 children and adolescents with chronic kidney disease (CKD); (29 CKD stage 2-4, pre-dialysis group & 29 CKD stage 5, dialysis group) & 29 age & gender matched controls were enrolled in the current cross-sectional study. Homeostasis model assessment of insulin resistance (HOMA-IR) using fasting insulin & glucose, where IR was considered if HOMA-IR was ≥ 4.39. **Aim:** Detect hyperinsulinemia & IR in pediatric CKD patients. **Results:** Fasting insulin & glucose hadn't significantly changed between CKD patients & controls (p=0.7, 0.3 respectively), while IR represented by HOMA-IR was found in a total of 11 (12.6%) CKD patients (6, 6.89% CKD5d & 5, 5.74% CKD 2-4) with no significant difference between pre-dialysis & dialysis groups (p>0.05), while it was significant with controls (p= 0.0٣٩), meanwhile, the total means of HOMA-IR between were no statistically significant between all CKD patients & (p=0.64). HOMA-IR correlated positively to dialysis durations (p= <0.001, <0.001 respectively), but hadn't changed with BMI. **Conclusion:** Pre-dialysis & dialysis CKD pediatric patients are at a high risk of IR & hence CVD. CKD & dialysis durations are independent risk factors for IR.

Key words: BMI, CKD, HOMA-IR, IR

INTRODUCTION

Chronic Kidney Disease (CKD) is a major problem in most developed and developing countries, in which the prevalence continues to increase each year ***(Lozano et al., 2012).***

Chronic kidney disease, is a slow progressive loss of kidney function over a period of several years which goes undetected and undiagnosed until the disease is well advanced and the organ functions are seriously impaired, at which the patient will not survive without renal replacement therapy in the form of dialysis or a kidney transplant ***(KDIGO, 2012).***

Patient has chronic kidney disease if either of the following criteria are present:

1. Kidney damage for at least 3 months as defined by structural or functional abnormality of kidney with or without decreased glomerular filtration rate (GFR) manifested by 1 or more of the following features:

   a. Abnormalities in composition of blood or urine

   b. Abnormality in imaging tests

   c. Abnormality on kidney biopsy

2. Any patient who has a GFR of less than 60 mL/min per 1.73 m^2 lasting for 3 months with or without kidney damage ***(KDIGO, 2012).***

The KDIGO guidelines also classified CKD into five stages:

- Stage 1: Kidney damage with a normal or increased GFR (>90 mL/min per 1.73 m2)
- Stage 2: Mild reduction in the GFR (60 to 89 mL/min per 1.73 m2)
- Stage 3: Moderate reduction in the GFR (30 to 59 mL/min per 1.73 m2)
- Stage 4: Severe reduction in the GFR (15 to 29 mL/min per 1.73 m2)
- Stage 5: Kidney failure (GFR <15 mL/min per 1.73 m2 or dialysis)

Children who have CKD may present with a combination of problems involving growth, nutrition, electrolyte disturbances, renal osteodystrophy, anemia, hypertension, and renal replacement therapy related complications ***(KDIGO, 2012).***

Insulin resistance is a well-known complication of CKD, which is defined as reduced sensitivity of target organs to the biologic effects of insulin. Major functions of insulin include stimulation of glucose uptake by skeletal muscles, inhibition of hepatic glucose production, and inhibition of lipolysis in adipose tissues ***(Stumvoll et al., 2005; Fliser et al., 2006).***

Although exact mechanisms of insulin resistance in CKD remain to be elucidated, a post receptor defect has been recognized as the primary defect in CKD. Other mechanisms

include chronic inflammation, excess visceral fat, adipokine deregulation and accumulation, metabolic acidosis, oxidative stress, vitamin D deficiency, anemia, decreased physical activity, and accumulation of uremic toxins ***(Kalantar-Zadeh et al., 2004; Trirogoff et al., 2007).***

Insulin resistance is a major risk factor contributing to cardiovascular disease through endothelial dysfunction, oxidative stress, dyslipidemia, systemic inflammation, and activation of the renin–angiotensin–aldosterone system. Insulin resistance is measured by using the homeostasis model assessment for insulin resistance (HOMA-IR) will be calculated as: fasting insulin (microU/L) × fasting glucose (nmol/L)/22.5 ***(Wallace et al., 2008).***

Also, it has been linked to accelerated protein catabolism leading to protein energy wasting and malnutrition ***(Siew et al., 2010).***

Therefore, insulin resistance may be an important therapeutic target for reduction of cardiovascular mortality in patients with CKD ***(Rutter et al., 2005).***

Leptin is the most abundant hormone produced by adipocytes, which plays key roles in the regulation of glucose homeostasis and insulin sensitivity ***(Vianna et al., 2012).***

Higher leptin levels were shown to be associated with obesity, dyslipidemia, insulin resistance, hypertension and

inflammatory states and reflects compromised adipose tissue function that has been shown to be a predictor of cardiovascular diseases and mortality in in CKD patients ***(Wannamethee et al., 2007; Berglund et al., 2012).***

Serum leptin levels in CKD pediatric patients remain controversial especially in pediatric patient and its full pathophysiology with insulin resistance in CKD patients not yet clearly understood ***(Nehus et al., 2014).***

AIM OF THE WORK

1) **Primary objective**: To detect insulin resistance in different stages of CKD by HOMA-IR & study leptin level in CKD patients.

2) **Secondary objective:** To study the link between insulin resistance and leptin level on cardiovascular Function in CKD pediatric patients.