Resistin level and its relation with glucose metabolism in children with chronic renal insufficiency and undergoing hemodialysis

Thesis

Submitted for the partial fulfillment of Master degree in Clinical and Chemical Pathology

by
Sherif Mofeed Megalla Ekladious
MB.B.CH

Supervised by

Professor Dr. Ola Abd El Monem El Sissy
Professor of Clinical and Chemical Pathology
Faculty of medicine – Cairo University

Professor Dr. Hebat Allah M. Sharaf El Deen
Assistant professor of Clinical and Chemical Pathology
Faculty of medicine – Cairo University

Dr. Samar Mohamed Sabry Ahmed
Lecturer of Pediatrics
Faculty of medicine – Cairo University

Faculty of medicine
Cairo University
2008

Acknowledgment

First and foremost, thanks are due to ***ALLAH****, the most merciful and benevolent for his gifts to all of us.*

I would like to thank my family who always provide me with love, care and support.

I would like to express my deepest gratitude to ***Professor Dr. Ola Abd El Monem El Sissy*** *Professor of Clinical and Chemical Pathology, Faculty of medicine, Cairo Universityfor her great support and guidance throughout the preparation of this work.*

Words fail to express my thanks to ***Professor Dr. Hebat Allah M. Sharaf El Deen*** *Assistant professor of Clinical and Chemical Pathology, Faculty of medicine, Cairo University as she honored me with her patience and invaluable assistance that helped me to accomplish this work.*

Also I am deeply grateful to ***Dr. Samar Mohamed Sabry Ahmed*** *Lecturer of Pediatrics, Faculty of medicine, Cairo University who packed me with her knowledge amd experience throughout the work.*

Abstract:

Background :

Resistin is a newly discovered peptide that inhibits adipogenesis. Furthermore, it may be involved in the regulative processes taking place in insulin resistance and inflammation.

Aim :

The aim of the present study was (1) to evaluate the serum concentration of resistin in the children with chronic renal insufficiency (CRI) & those on hemodialysis and (2) to investigate the possible impact of resistin on the insulin resistance.

Methods :

In total, 20 patients (10 patients with chronic renal insufficiency and 10 patients on hemodialysis) and 10 healthy age and sex matched control subjects were included in the study.

Resistin conc. was measured by ELISA, insulin resistance was obtained from homeostasis model assessment of insulin resistance (HOMA-IR)

Results :

Resistin conc. was significantly elevated in hemodialysis patients (16.2 (14.25-27.6) ng/ml) and in CRI patients (14.7 (8.1-22.8) ng/ml)in comparison to controls (6.6 (6.15-8.92) ng/ml) (P-value = 0.002)

There was no significant correlation between resistin level and HOMA-IR, BMI or lipid profile.

Conclusion :

Resistin level was increased in children with renal failure. However, this elevation was not found to be associated with insulin resistance.

Key words:

Resistin – chronic renal failure – hemodialysis – children.

List of Abbreviations

BAT :	Brown adipose tissue.
BMI :	Body mass index.
BUN :	Blood urea nitrogen.
CAC :	Coronary artery calcification.
CAD :	Coronary artery disease.
c-AMP :	Cyclic adenosine monophosphate.
HOMA-IR :	homeostasis model assessment of insulin resistance.
CRF :	Chronic renal failure.
CRI :	Chronic renal insufficiency.
CRP :	C-reactive protein.
ELISA :	Enzyme linked immuno sorbant assay.
ESRD :	End stage renal disease.
ET-1 :	Endothelin-1.
FBS :	Fasting blood sugar
FIZZ-1 :	Found in inflammatory zone-1.
FSGS :	Focal segmental glomerulosclerosis.
GFR :	Glomerular filteration rate.
HDL-c :	High density lipoprotein-cholesterol
HGO :	Hepatic glucose output.
IL-6 :	Interleukin-6.
IRS-1 :	Insulin receptor substrate-1.
IVP :	Intravenous pyelography.
LDL-c :	Low density lipoprotein-cholesterol.
LPS :	Lipopolysaccharides.
LVH :	Left ventricular hypertrophy.
mRNA :	Messenger ribonucleic acid.
MSG :	Monosodium glutamate.

NPY :	Neuropeptide Y
OA :	Osteoarthritis.
PPAR-γ :	Peroxisome proliferator-activated receptor γ.
RA :	Rheumatoid arthritis.
RELMs :	Resistin-like molecules
RT-PCR :	Reverse transcription polymerase chain reaction.
SOCS-3 :	Suppressor of cytokine signaling 3.
TNF-α :	Tumor necrosis factor α.
TZD :	Thiazolidinediones.
WAT :	White adipose tissue.

INTRODUCTION

Adipose tissue is no longer regarded as a passive depot of energy excess storage in the form of triglycerides, but as a tissue that actively secretes proteins such as leptin, adiponectin and newly described molecule resistin with various autocrine/paracrine functions, such as body weight regulation and glucose and lipid homeostasis ***(Mora et al,2002; Axelsson et al,2005; Gimeno et al,2005***; ***Yudkin et al,2005)***.

Human resistin is a cysteine-rich, 108-amino-acid peptide hormone with a molecular weight of 12.5 kDa ***(Nusken et al,2006)*** expressed in human adipose tissue and the initial suggestion that it might be implicated in the development of insulin resistance has recently been challenged. Data regarding serum resistin concentrations in humans are scarce and a large population study to clarify its role in humans is still lacking.

Recently, high levels of resistin have been reported in adult patients with CRF ***(Kielstein et al,2003).*** Resistin may represent a mechanism linking insulin resistance to cardiovascular disease developed in CRF ***(Diez et al,2005).***

AIM OF THE WORK

The aim of the present study is to evaluate the serum concentration of resistin in the children with chronic renal insufficiency (CRI) & those on hemodialysis and to investigate the possible impact of resistin on the insulin resistance.

CHAPTER (1)
CHRONIC RENAL FAILURE

Introduction

Chronic renal failure (CRF) is defined as an irreversible reduction in the glomerular filteration rate (GFR). Progressive renal disease occurs in all age groups. The incidence of chronic renal insufficiency among children is approximately 18 per million **(*Vogt et al,2004).***

Stages of Chronic Kidney Diseases

The term chronic renal failure is used to describe the stage of renal dysfunction ranging from mildly decreased glomerular filteration rate (GFR about 75 ml/min/1.73m^2) to severely affected (GFR about 10 ml/min/1.73m^2). This is the stage during which medications are used to treat the effects of renal dysfunction, while the term end-stage renal disease (ESRD) is used to describe the phase when patient's renal dysfunction has progressed to the point at which homeostasis and ultimately survival cannot be sustained with native renal function, and either dialysis or renal transplantation is required ***(Harmon,1999).***

Renal insufficiency is described when GFR is < 50% of normal, CRF is described when GFR is < 25% of normal. At the advanced stage of reduced GFR, the body cannot adapt the different metabolic changes,

and therefore by that time different clinical manifestations appear as acidosis, growth failure, renal osteodystrophy, hypertension and anemia ***(Chan et al,1994).***

However, the term CRF is often applied broadly to all patients with chronic deterioration in renal function ***(Kanwal et al,1992)***

Stages of chronic kidney disease

Stage	Description	GFR (mL/min/1.73 m^2)
1	Kidney damage with normal or increased GFR	> 90
2	Kidney damage with mildly decreased GFR	60–89
3	Moderately decreased GFR	30–59
4	Severely decreased GFR	15–29
5	Kidney failure	< 15 (or dialysis)

From National Kidney Foundation, KDOQI, chronic kidney disease guidelines

Etiology

Congenital structural anomalies, including reflux, obstruction, hypoplasia, and dysplasia are the principal underlying causes of end-stage renal disease, particularly in the very young child. Older children also develop end-stage renal disease from glomerulopathies, including focal segmental glomerulosclerosis (FSGS), hemolytic uremic syndrome, immune complex diseases, and hereditary nephropathies, such as Alport's disease ***(Foreman et al,1988).*** Although diabetic nephropathy does not result in chronic renal insufficiency in childhood, most patients with diabetes who develop end-stage renal disease in their 20s and 30s are

those whose diabetes presented during childhood. The prognosis for the infant, child, or adolescent with CRF has improved dramatically over the past 4 decades because of improvements in medical management (aggressive nutritional support, recombinant erythropoietin, and recombinant growth hormone), dialysis techniques, and renal transplantation ***(Avner et al,2004).***

Chronic renal failure in Egyptian children less than 5 years of age is attributed to parenchymatous disease in 73% of cases and obstructive etiology in 27% of cases, while after 5 years of age , parenchymatous disease is the cause in 67% and obstructive etiology constitutes 33% of cases ***(Safouh,1996).***

Major causes of chronic renal failure

I) Glomerulopathies:
- A- Primary glomerular diseases: (81%)
  1- Focal and segmental glomerulosclerosis
  2- Membranoproliferative glomerulonephritis
  3- IgA nephropathy
  4- Membranous nephropathy
- B-Secondary glomerular diseases: (19%)
  1- Diabetic nephropathy
  2- Amyloidosis
  3- Post infectious glomerulonephritis
  4- HIV-associated nephropathy
  5- Collagen vascular diseases
  6- Sickle cell nephropathy
  7- HIV-associated membranoproliferative glomerulonephritis

II) Tubulointerstitial nephritis
  1- Drug hypersensitivity
  2- Heavy metals
  3- Analgesic nephropathy
  4- Reflux/chronic pyelonephritis
  5- Idiopathic

III) Hereditary diseases
  1- Polycystic kidney disease

2- Medullary cystic disease
3- Alport's syndrome

IV) Obstructive nephropathies
1- Prostatic disease
2- Nephrolithiasis
3- Retroperitoneal fibrosis/tumor
4- Congenital

V) Vascular diseases
1- Hypertensive nephrosclerosis
2- Renal artery stenosis

(Lawrence et al,2006)

Pathogenesis

The remarkably similar histologic appearance of chronic renal diseases regardless of the primary insult suggests a common final pathway, with variations dependent on unique disease-specific factors and individual susceptibility. The alterations and adaptations in nephrons remaining after the initial insult are thought ultimately to cause scarring and further nephron loss, thus perpetuating a vicious cycle that results in the end-stage kidney. However, individual genetic variations and disease-specific mechanisms contribute to variability in progression and response to therapy ***(Jungers et al,1995)***. Possible mechanisms of progressive renal damage include, but are not limited to, hemodynamic factors, shear stress, growth factors, cell-specific damage, and metabolic factors such as diabetes and hyperlipidemia.

Pathophysiology

Pathophysiology of CRF is summarized in the following table:

Manifestation	Mechanisms
Accumulation of nitrogenous waste products	Decrease in glomerular filtration rate
Acidosis	Decreased ammonia synthesis Impaired bicarbonate reabsorption Decreased net acid excretion
Sodium retention	Excessive renin production Oliguria
Sodium wasting	Solute diuresis Tubular damage
Hyperkalemia	Decrease in glomerular filtration rate Metabolic acidosis Excessive potassium intake Hyporeninemic hypoaldosteronism
Renal osteodystrophy	Impaired renal production of 1,25-dihydroxycholecalciferol Hyperphosphatemia Hypocalcemia Secondary hyperparathyroidism
Growth retardation	Inadequate caloric intake Renal osteodystrophy Metabolic acidosis Growth hormone resistance Anemia
Anemia	Decreased erythropoietin production Iron deficiency Folate deficiency Vitamin B12 deficiency Decreased erythrocyte survival
Bleeding tendency	Defective platelet function
Infection	Defective granulocyte function Impaired cellular immune functions Indwelling dialysis catheters
Neurologic symptoms (fatigue, poor concentration, headache, drowsiness, memory loss, seizures, peripheral neuropathy)	Uremic factor(s) Aluminum toxicity Hypertension
Gastrointestinal symptoms (feeding intolerance, abdominal pain)	Gastroesophageal reflux Decreased gastrointestinal motility
Hypertension	Volume overload Excessive renin production
Hyperlipidemia	Decreased plasma lipoprotein lipase activity
Pericarditis/cardiomyopathy	Uremic factor(s) Hypertension Fluid overload
Glucose intolerance	Tissue insulin resistance

(Vogt et al,2004)

Presentation of the child with CRF

Patients with CRF may pass a silent or a misdiagnosed course of illness and then present by acute renal failure. Up to 40-50% of patients presenting with ESRD are not aware of any pre-existing renal disease ***(Abuelo et al,1989).***

The most common finding that should alert the pediatrician to the possibility of chronic renal disease is growth impairment, short stature, particularly if associated with other symptoms such as polyuria, frequent bouts of dehydration, salt craving, bone deformities, abnormal teeth development or anemia. A previous history of urinary tract infection or glomerulonephritis adds further support to this suspected diagnosis ***(Oski et al,1994).***

Symptoms and Signs of CRF

I) Gastrointestinal:
1- Anorexia, nausea and vomiting.
2- Dysgnesia (abnormal taste).
II) Neuromuscular:
1- Lethargy and fatigue.
2- Inability to concentrate.
3- Reversal of sleep.
4- Restless leg.
5- Convulsions.
6- Stupor, coma.
7- Peripheral neuropathy.
III) Endocrine:
1- Amenorhoea.
2- Reduced libido.
3- Reduced fertility.
IV) Cardiac:
1- Volume overload.
2- Pericarditis and tamponade.
V) Hematologic:

1- Anemia.
2- Bleeding (platelet defect)

VI) Bone:
1- Pain.
2- Pathological fractures
3- Impaired growth.

VII) Dermatologic:
1- Itching

(Abuelo et al,1989)

Assessment of CRF

A- Clinical assessment:

A complete history and physical examination including fundoscopic examination ***(Trompeter,1987).***

B- Laboratory assessment

Laboratory assessment in patients with CRF include blood urea nitrogen, serum creatinine, electrolytes (calcium and phosphorous), alkaline phosphatase, serum albumin, 24-hour urine electrolyte, complete blood count with evaluation of blood smear and RBCs indices, fasting triglycerides, cholesterol and serum uric acid ***(Reimold,1981).***

The degree of renal dysfunction may be determined by applying the Schwartz formula, which provides an estimation of patient's GFR:

GFR (ml/min/1.73m^2) = k × Height (cm) / serum creatinine (mg/dl)

(where k is 0.33 for low-birthweight infants younger than 1 yr, 0.45 for infants younger than 1 yr, 0.55 for children and adolescent females, and 0.70 for adolescent males). ***(Williams et al,2002)***.

C- Radiological assessment:

- Chest and bone x-ray.
- Renal ultrasound.
- Radioscopic scanning (dynamic and static).
- Intravenous pyelography (IVP).
- Ascending and micturating cystourethrogram.
- Echocardiography. ***(Kanwal et al,1992)***