Serum Uric Acid Level and Endothelial Dysfunction in Patients with Nondiabetic Chronic Kidney Disease

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By

Ahmed Abdelmoneim Abdelmageed Emara
M.B, B.Ch (Faculty of Medicine – Ain Shams University)

Under Supervision Of

Prof. Dr. Eman Ibrahem Sarhan
Professor of Nephrology and Internal Medicine
Faculty of Medicine – Ain Shams University

Dr. Hesham Atef Abo-Eleil
Assistant Professor of Nephrology
and Internal Medicine
Faculty of Medicine – Ain Shams University

Dr. Eman Ahmed Shawky Geneidi
Assistant Professor of Radiodiagnosis
Faculty of Medicine – Ain Shams University

Faculty of Medicine
Ain Shams University
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توطئة للحصول على درجة الماجستير فى امراض الباطنة العامة

مقدمة من

الطبيب / احمد عبد المنعم عبد المجيد عمارة

بكالوريوس الطب والجراحة

تحت إشراف

الأستاذ الدكتور/ إيمان ابراهيم سرحان

أستاذة الباطنة العامة والكلى
كلية الطب - جامعة عين شمس

أستاذ م. دكتور/ هشام عاطف ابوالليل

أستاذ مساعد الباطنة العامة والكلى
كلية الطب - جامعة عين شمس

استاذ م. دكتور/ إيمان احمد شوقى جنيدى

أستاذ مساعد الأشعة التشخيصية
كلية الطب - جامعة عين شمس

كلية الطب

جامعة عين شمس

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قال العماد الأصفهاني:

" إني رأيتُ أنه لا يكتب أحد كتاباً في يومهِ إلا قال فيغَدِهِ: لوغُيِّرَ هذا لكان أحسن ولو زيد هذا لكان يُستحَسن ولو قُدّم هذا لكان أفضل ولو تُرِك هذا لكان أجمل. وهذا أعظم العبر وهو دليل على استيلاء النقص على جملة البشر "

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List of Abbreviations

A2	Angiotensin II
AASK	African American Study of Kidney Disease and Hypertension
ACE	Angiotensin Converting Enzyme
ADMA	Asymmetric dimethylarginine
AGE`s	Advanced glycation endproducts
AHS	Allopurinol Hypersensitivity Syndrome
AIPRD	ACE Inhibition and Progressive Renal Disease
AP-1	Activator Protein 1
APEX	Allopurinol Placebo controlled Efficacy study of febuXostat
ARB	Angiotensin Receptor Blocker
ARIC	Atherosclerosis Risk in Communities
AV	Arterio venous
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CAM	Chorio Allanotic Melanoma
Ccr	Creatinine Clearance
CDC	Centers for Disease Control and Prevention
CHS	Cardiovascular Health study
CKD	Chronic Kidney Disease
COX-2	Cycloxygenase-2
CRP	C-Reactive Protein
DM	Diabetes Mellitus
EBPG	European Best Practice Guidelines
eGFR MDRD	MDRD estimated GFR
EPC	Endothelial pro-generator cell
EPO	Erythrppiotein
ESRD	End Stage Renal Disease
FACT	Febuxostat versus Allopurinol Controlled Trial
FDA	Food and Drug Administration
FMD	Flow-Mediated Dilation

GFR	Glomerular Filtration Rate
GPV	Platelet Glycoprotein V
HbA1c	Glycated Haemoglobin
HDLc	High Density Lipoprotein cholesterol
Hgb	Haemoglobin
HGRPT	Hypoxanthine Guanine phosphoribosyl Transferase
HTN	Hypertension
ICAM-1	Intercellular Adhesion Molecule-1
IDEAL	Initiating dialysis early & late
IgA	Immunoglobulin A
IL	Interleukin
IL-1B	Interleukin -1B
JNC7	Journal of national committee 7
LDLc	Low Density Lipoprotein cholesterol
LIFE study.	Losartan intervention For Endpoint Reduction study
LVH	Left ventricular Hypertrophy
MAP	Mitogen Activated Protein
MCF-1	Monocyte Chemoattractant Factor **-1**
MDRD	Modification of Diet in Renal Disease
MRFIT	Multiple Risk Factor Intervention Trial
MSU	Monosodium Urate
NF-KB	Nuclear Factor Kappa B
NHANES	National Health and Nutrition Examination Survey
NO	Nitric Oxide
NSAIDs	Non Steroidal Anti-inflammatory Drugs
OAT	Organic Anion Transporter
PAI-1	Plasminogen Activator Inhibitors
PDGF	Platelet Drived Growth Factor
PKC	Protein kinase C
PRPS	Phosphoribosyl Pyrophosphate synthetase
PTH	Parathyroid Hormone
RRT	Renal replacement Therapy

SPC	Smooth muscle progenerator cell
TBARS	Thiobarbituric acid-reactive substances
TFP-I	Tissue Factor Pathway Inhibitors
TNF	Tumor Necrosis Factor
t-PA	Plasminogen Activator
TSAT	Transferrin Saturation
TWEAK	TNF-like Weak Inducer of Apoptosis
TXA2	Thromboxane A_2
URAT1	Urate Transporter 1
US	United States
VCAM-1	Vascular Adhesion Molecule -1
vWF	Von Willebrand factor

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Introduction

Patients with chronic kidney disease (CKD) often manifest endothelial dysfunction, which is usually defined as a defect in endothelial nitric oxide (NO) bioavailability ***(Baylis, 2008)***.

At the same time, endothelial dysfunction has emerged as an important risk factor for progression of kidney disease ***(Baylis, 2008)***.

In the remnant kidney model, an experimental model of CKD, the degree of endothelial dysfunction is an important predictor for progression of kidney disease ***(Ochodnicky et al., 2006)***.

Other studies have also shown that a lack of endothelial NO can accelerate both non-diabetic and diabetic kidney disease as well as aging-related renal disease in laboratory mode ***(Nakayama et al., 2010)***.

Endothelial function, as determined by the dilation of the brachial artery following transient occlusion (FMD), is inversely correlated with serum uric acid levels in subjects with asymptomatic hyperuricemia as well as in hyperuricemia associated with essential hypertension (HTN) ***(Zoccali et al., 2006)***.

Endothelial function and structural arterial changes can be measured noninvasively with high-resolution ultrasound to measure brachial artery flow-mediated dilatation (FMD) and carotid artery intima-media thickness (cIMT), respectively ***(Lorenz et al., 2007)***.

Conversely, reducing uric acid with a xanthine oxidase inhibitor improves endothelial function in subjects with asymptomatic hyperuricemia as well as in association with a wide variety of conditions, including diabetes, heart failure, or sleep apnea syndrome ***(El Solh et al., 2006)***.

Nevertheless, no study has examined the relationship between uric acid and endothelial function in subjects with CKD. This is important as it is recognized that CKD may be associated with other conditions that potentially reduce endothelial function, including oxidative stress and circulating NO synthase inhibitors ***(Baylis, 2008).***

Aim of the Work

This work aims to study the association between serum uric acid level and endothelial dysfunction in patients with non diabetic chronic kidney disease.

Chronic kidney Disease

All patients with renal disease (whether acute or chronic) should undergo an assessment of renal function by estimating the glomerular filtration rate (GFR). This measurement is used clinically to evaluate the degree of renal impairment, to follow the course of the disease, and to assess the response to therapy. An attempt must also be made to obtain a specific diagnosis. The first step in this process is a careful urinalysis ***(Theodore et al., 2010).***

Chronic kidney disease (CKD) is a worldwide public health problem. In the United States (US), the prevalence of end stage renal disease (ESRD) is increasing ***(National Kidney Foundation, 2002).***

Although the exact reasons for the growth of the ESRD program are unknown, changes in the demographics of the population, differences in disease burden among racial groups and under-recognition of earlier stages of CKD and of risk factors for CKD, may partially explain this growth ***(Obrador et al., 2002).***

Patients with ESRD consume a disproportionate share of health care resources. The total cost of the ESRD program in the US was approximately $39.46 billion in 2008. Medicare costs per person per year were nearly $66,000 overall, ranging from $26,668 for transplant patients to $77,506 for those

receiving hemodialysis therapy *(**USRDS Annual Data Report, 2010**)*.

Adaptive hyperfiltration, although initially beneficial, appears to result in long-term damage to the glomeruli of the remaining nephrons, which is manifest by proteinuria and progressive renal insufficiency. This process appears to be responsible for the development of renal failure among those in whom the original illness is either inactive or cured ***(Abboud and Henrich, 2010).***

Not all individuals have progressive loss of kidney function. Some studies show a high rate of progression, while others report relatively stable disease ***(Hallan et al., 2006)***.

The rate of progression of CKD from one major stage to another varies based upon the underlying disease, presence or absence of comorbid conditions, treatments, socioeconomic status, individual genetics, ethnicity, and other factors. Using epidemiologic data, general estimates for the rate of transition from a GFR between 15 to 60 mL/min per 1.73 m2 to end stage disease may be approximately 1.5 percent per year, while the rate of transition from a GFR above 60 to below 60 mL/min per 1.73 m2 may be approximately 0.5 percent per year **(*Fox et al., 2004*).**

The combination of both a low GFR plus dipstick positive proteinuria, versus either parameter alone, is associated with a significantly increased risk of progressive renal disease.