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Putative Role of Fibroblast Growth Factor 23 in Diagnosis of Chronic Kidney Diseases in Human

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List of Contents

Subject	*Page No.*
List of Abbreviations	**i**
List of Tables	**iii**
List of Figures	**iv**
Abstract	
1. Introduction	**1**
Aim of the Work	**3**
2. Review of Literature	**4**
3. Subjects and Methods	**26**
4. Results	**43**
5. Discussion	**63**
6. Summary	**74**
7. Conclusion	**78**
References	**79**
الملخص العربى	**ـــ**
المستخلص العربى	**ـــ**

List of Abbreviations

Abbr.		Full-term
ALT	**:**	Alanine aminotransferase
AST	**:**	Aspartate aminotransferase
BCP	**:**	Bromocresol purple
BUN	**:**	Blood urea nitrogen
CKD-EPI	**:**	Chronic kidney disease epidemiology collaboration
CK	**:**	Creatine kinase
CKD	**:**	Chronic kidney disease
CRF	**:**	Chronic renal failure
CRP	**:**	C-Reactive protein
EDTA	**:**	Ethylene diamine tetra acetic acid.
eGFR	**:**	Estimated glomerular filtration rate
Egr-1	**:**	Early growth response factor 1
FGF23	**:**	Fibroblast growth factor 23
FGF-Rs	**:**	Fibroblast growth factor receptors
G6PDH	**:**	Glucose-6-phosphate dehydrogenase
GPO	**:**	Glycero phosphate oxidase
GSH	**:**	Reduced Glutathione
GSSG	**:**	Oxidized Glutathione
HCC	**:**	Hepatocellular carcinoma
HCV	**:**	Hepatitis C Virus
HDL-Chol.	**:**	High Density Lipoprotein Cholesterol
HIV	**:**	Human immunodeficiency virus
HK	**:**	hexokinase
HMG-CoA	**:**	3-hydroxy 3-methyl glutaryl CoA
HOMA-IR	**:**	Homeostasis model assessment
HPO	**:**	Horseradish peroxidase
I/IGF1	**:**	Insulin/insulin-like growth factor
IBD	**:**	Inflammatory bowel disease

IDDM	**:**	Insulin dependent diabetes mellitus
IDF	**:**	International diabetes federation
IDL	**:**	Intermediate density lipoprotein
IL	**:**	Interleukine
IR	**:**	Insulin resistance
IRS-1	**:**	Insulin receptor substrate-1
LCAT	**:**	Lecithin-cholesterol acyltransferase
LDH	**:**	Lactate dehydrogenase
LDL-Chol.	**:**	Low Density Lipoprotein Cholesterol
MDH	**:**	Malate dehydrogenase
MDRD	**:**	Modification of diet in renal disease
NAD	**:**	Nicotinamide Adenine Dinucleotide
NIDDM	**:**	Non-insulin dependent diabetes mellitus
NIH	**:**	National institutes of health
NK cells	**:**	Natural killer cells
NPT2	**:**	Sodium-phosphate cotransporter 2
PTH	**:**	Parathyroid hormone
QS	**:**	Quantitation standard
RAAS	**:**	Renin-angiotensin-aldosterone
ROS	**:**	Reactive oxygen species
SH	**:**	Sulfhydryl (thiol) group
SHPT	**:**	Secondary hyperparathyroidism
SREBP	**:**	Sterol regulatory element-binding protein
T-cells	**:**	T-lymphocytes
T-chol.	**:**	Total cholesterol
TG	**:**	Triglyceride or triacylglyceride
TNF-α	**:**	Tumor necrosis factor- alpha
VLDL	**:**	Very-low-density lipoprotein

List of Tables

Table No.	Title	Page No.
(2.1):	Stages of Chronic kidney Disease	7
(4.1):	Effect of chronic kidney disease (CKD) on glomerular filtration rate (GFR) (mL/min) and glucose (mg/dL)	44
(4.2):	Effect of chronic kidney disease (CKD) on kidney functions in human.	47
(4.3):	Effect of chronic kidney disease (CKD) on serum calcium and phosphorus levels.	50
(4.4):	Effect of chronic kidney disease (CKD) on liver functions.	52
(4.5):	Effect of chronic kidney disease (CKD) on serum activities of creatine kinase (CK) (U/mL) and lactate dehydrogenase (LDH) (U/L).	55
(4.6):	Effect of chronic kidney disease (CKD) on serum level of parathyroid hormone (PTH) (pg/mL) and testosterone (ng/mL)	58
(4.7):	Effect of chronic kidney disease (CKD) on C- reactive protein (CRP) (mg/dL) & serum level of tumor necrosis factor alpha (TNF-a) (pg/mL) and fibroblast growth factor-23 (FGF-23) (pg/mL).	61

List of Figures

Figure No.	Title	Page No.
(2.1):	Simplified scheme of the development of secondary Hyperparathyroidism	24
(3.1):	standard curve for human free testosterone (pg/mL)	38
(3.2):	Standard curve of tumor necrosis factor (TNF)-α	40
(3.3):	Standard curve of FGF-23	41
(4.1):	Effect of chronic kidney disease (CKD) on glomerular filtration rate (GFR) (mL/min)	44
(4.2):	Effect of chronic kidney disease (CKD) on serum level of glucose (mg/dL)	42
(4.3):	Effect of chronic kidney disease (CKD) on serum level of creatinine (mg/dL)	47
(4.4):	Effect of chronic kidney disease (CKD) on serum level of blood urea nitrogen (BUN) (mg/dL)	48
(4.5):	Effect of chronic kidney disease (CKD) on serum level of albumin (g/dL)	48
(4.6):	Effect of chronic kidney disease (CKD) on serum level of calcium (mg/dL)	50
(4.7):	Effect of chronic kidney disease (CKD) on serum level of phosphorus (mg/dL)	51
(4.8):	Effect of chronic kidney disease (CKD) on serum activity of alanine aminotransferase (ALT) (U/L)	53

(4.9): Effect of chronic kidney disease (CKD) on serum activity of aspartate aminotransferase (AST) (U/L) 53

(4.10): Effect of chronic kidney disease (CKD) on serum ALT/AST ratio 54

(4.11): Effect of chronic kidney disease (CKD) on serum activity of creatinine kinase (CK) (U/mL) 56

(4.12): Effect of chronic kidney disease (CKD) on serum activity of lactate dehydrogenase (LDH) (U/L) 56

(4.13): Effect of chronic kidney disease (CKD) on serum level of parathyroid hormone PTH (pg/mL) 58

(4.14): Effect of chronic kidney disease (CKD) on serum level of testosterone (pg/mL) 59

(4.15): Effect of chronic kidney disease (CKD) on serum level of Creactive protein (CRP) (mg/dL) 61

(4.16): Effect of chronic kidney disease (CKD) on serum level of tumor necrosis factor alpha (TNF-a) (pg/mL) 62

(4.17): Effect of chronic kidney disease (CKD) on serum level of fibroblast growth factor-23 (FGF-23) (pg/mL) 62

Abstract

Putative role of fibroblast growth factor 23 in diagnosis of chronic kidney diseases in human

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Keywords: Calcitropic hormones, CKD, FGF23, Inflammation, PTH

The present study aimed to evaluate the clinical utility of serum FGF23 as an early specific biomarker in the diagnosis and progression of chronic kidney disease (CKD) patients. A number of 120 male patients with CKD who were classified according to the estimated glomerular filtration rate (eGFR) into four stages (n=30 for each stage), in addition to 30 healthy control men were included. Patients in stage 2 of CKD did not show any significant difference in serum levels of urea and creatinine, and lactate dehydrogenase (LDH) activity. With the progression of CKD from stage 3 to stage 5, there were linear increases in the serum urea and creatinine levels, and LDH activity. There was a significant decrease in serum albumin and significant elevation in creatine kinase in all CKD stages. There was a significant decrease in serum

Ca^{2+} level in stages 2-4. Only patients in CKD stage 5 showed a significant elevation in serum phosphorus level. There were significant elevations in serum aminotransferases (ALT and AST), C-reactive protein, and parathyroid hormone levels in stages 4 and 5. Serum testosterone level was significantly reduced in stages 3 and 4 as compared to control. With the progression of CKD stages from stage 2 to 5, there were linear significant elevations in serum tumor necrosis factor-α (TNF-α) and FGF23 levels. To conclude, FGF23 was the most sensitive indicator in the early diagnosis and staging of CKD. Other biomarkers were elevated only in the late stages of CKD, in addition to their low specificity. Therefore, FGF23 could be used in the diagnosis and prognosis of CKD patients.

Introduction

The incidence of chronic kidney disease (CKD) is reaching an epidemic proportion worldwide. The number of patients with earlier stages of CKD exceeds those reaching end-stage renal disease by more than 50-folds **(El-Nahas and Bello, *2005)***. Recent professional guidelines classify the severity of CKD into five stages starting with stage 1, being the mildest and usually causing few symptoms, to stage 5, being a severe illness with poor life-expectancy if untreated **(National Kidney Foundation*, 2002)***.

Early identification of CKD and timely detection of progression are truly global challenges facing the nephrology community, especially since a number of promising primary and secondary interventions to accelerate progression are available **(El-Nahas and Bello, 2005)**. In humans, fibroblast growth factor 23 (FGF23) is a protein encoded by the FGF23 gene **(Yamashita *et al*., 2005).** FGF23 is a member of the fibroblast growth factor (FGF) family which is responsible for phosphate metabolism **(Fukumoto, 2008).** The main function of FGF23 seems to be regulation of phosphate concentration in plasma. FGF23 is secreted by osteocytes in response to elevated calcitriol. FGF23 acts on the kidneys, where it decreases the expression of a sodium-phosphate cotransporter (NPT2) in the proximal tubule **(Jüppner,**

2011). Thus, FGF23 decreases the reabsorption and increases excretion of phosphate

This study has been conducted on adult patients with chronic kidney disease (CKD) stages 2-5 and apparently healthy subjects serving as a control group, all of whom willingly participated in the study. They were classified according to modification of diet in renal disease (MDRD) equation for estimating glomerular filtration rate (eGFR) **(National Kidney Foundation, 2002)**.

Aim of the Work

To evaluate the clinical utility of serum FGF23 as a novel non-invasive and reliable independent marker of diagnosis and progression of renal disease in patients of non-diabetic CKD.