

Assessment of the association between neuropeptide Y and chronic kidney disease progression

Thesis

Submitted for partial fulfillment of Master Degree in Internal Medicine

By

Hend Ahmed Ibrahim Abouelsaad

(M.B, B.Ch.)

Under supervision of

Prof.Dr. Saeed Abdelwhab Saeed

Professor of internal medicine and nephrology

Faculty of Medicine -Ain Shams University

Dr.Haitham Ezzat Abdelaziz

Assistant Professor of internal medicine and nephrology

Faculty of Medicine -Ain Shams University

Dr. Nahla Mohamed Teama

Lecturer of internal medicine and nephrology

Faculty of Medicine -Ain Shams University

Faculty of Medicine

Ain Shams University

2019

وما أوتيتم من العلم الا قليلا

ACKNOWLEDGEMENT

I would like to express my deepest indebtedness, gratitude and sincere appreciation to **Prof. Dr Saeed Abdelwhab Saeed** professor of Internal Medicine and Nephrology, Faculty of medicine, Ain Shams University, for his valuable help, kind advice and close supervision during all steps of this work. It was great honor to me to do this study under his supervision.

I would also like to express my special appreciation and thanks to **Dr Haitham Ezzat Abdelaziz**, Assistant Professor of internal medicine and nephrology Faculty of Medicine -Ain Shams University, who has been a tremendous mentor for me. I would like to thank him for encouraging my research.

I owe special feeling of gratitude to **Dr Nahla Mohamed Teama**, Lecturer of Internal Medicine and Nephrology, Faculty of Medicine, Ain Shams University who generously aided and directed me. Many thanks for her encouragement, supervision, cooperation, and helpful suggestions. She followed the procedures of the work with indispensable support, devotion.

Finally I like to say a heartfelt thank you to my Mum, Dad, Husband and Son for always believing in me and encouraging me to follow my dreams and for helping in whatever way they could during this challenging period

List of contents

Title	Page number
List of tables	4
List of figures	5
List of abbreviations	7
Abstract	10
Introduction	13
Aim of the work	18
Review of Literature	20
1) Chronic kidney disease	21
1) Definition	21
2) Pathology	21
3) Aging and renal function	23
4) Pathophysiology	23
5) Etiology	30
6) Presentation	32
7) Diagnosis and workup	36
8) Prognosis & Management	45
2. Chronic kidney disease biomarkers	60
Subjects and methods	79
Results	89
Discussion	116
Conclusion	123
Summary	127
References	130
Arabic summary	152

List of tables

Tables of Results

Title of the table	Page number
Demographic data group I and II	90
Primary renal disease in group I	92
Laboratory data group I and II	93
Laboratory data group Ia and Ib	101
ACEI/ARBs in group I and II	105
Insulin in group I and II	105
LLd in group I and II	107
Diuretics in group I and II	107
Comparison between group Ia and Ib as regard ACEI and insulin	108
Serum NpY in group Ia and Ib	109
CKD stages in group Ia and Ib	110
BMI in group Ia and Ib	110
SBP in group Ia and Ib	111
DBP in group Ia and Ib	111
Correlations between NpY and other variables in group Ia	112
Correlations between NpY and other variables in group Ib	113
ROC curve	114

List of figures

Figures of Results

Title of the figure	Page number
BMI group I and II	91
HTN group I and II	91
DM group I and II	92
Primary renal disease percentage in group I	92
Serum creatinine group I and II	94
Blood urea group I and II	94
eGFR group I and II	95
Serum NpY group I and II	95
Serum Na group I and II	96
Serum K group I and II	96
Serum Ca group I and II	97
Serum albumin group I and II	97
Urinary PCR group I and II	99
Protein in urine group I and II	99
WBC group I and II	100
Hb group I and II	100
Blood urea group Ia and Ib	101
Serum creatinine group Ia and Ib	101
eGFR group Ia and Ib	102
Serum NpY group Ia and Ib	102
Serum Na group Ia and Ib	103

Hb group Ia and Ib	105
Insulin in group I and II	106
Diuretics in group I and II	108
Serum NpY in group Ia and Ib	109
SBP in group Ia and Ib	111
DBP in group Ia and Ib	112
ROC curve analysis	115

Abbreviations

List of abbreviations

ACEI	Angiotensin Converting Enzyme Inhibitor	NICE	National Institute for Health and Clinical Excellence
ACP	American College of Physicians	NKF	National Kidney Foundation
ACR	Albumin/Creatinine ratio	NpY	Neuropeptide Y
ADA	American Diabetes Association	TGF α 1	Transforming Growth Factor α 1
ADAMTS	A Disintegrin-Like and Metalloproteinase with Thrombospondin	TNF	Tumour Necrosis Factor
ADMA	Asymmetric Dimethyl Arginine	kDa	kiloDalton
ADPKD	Autosomal Dominant Polycystic Kidney Disease	KDIGO	Kidney Disease: Improving Global Outcomes
AER	Albumin Excretion Rate	KDOQI	Kidney Disease Outcomes Quality Initiative
AKI	Acute Kidney Injury	KIM-1	Kidney Injury Molecule-1
ANA	Antinuclear antibodies	MDRD	Modification of Diet in Renal Disease
ARBs	Angiotensin II-Receptor Blockers	mEq	Milliequivalent.
ASN	American Society of Nephrology	mmol/L	Millimoles per Liter
ATP	Adenosine TriPhosphate	MPGN	MembranoProliferative GlomeruloNephritis
BMI	Body Mass Index	MRI	Magnetic resonance imaging
BUN	Blood urea nitrogen	NaHCO ₃	Sodium Bicarbonate
cANCA	cytoplasmic Anti-Neutrophil Cytoplasmic	NGAL	Neutrophil Gelatinase-Associated Lipocalin

	Antibodies		
CBC	Complete Blood Count		
CKD	Chronic Kidney Disease		
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration	NNT	Number Needed to Treat
CKD-MBD	CKD–Mineral and Bone Disorder	NO	Nitric Oxide
CrCl	Creatinine Clearance	NSAIDs	Non-steroidal anti-inflammatory drugs
CT	Computed tomography	OSA	Obstructive Sleep Apnea
CVD	Cardiovascular Disease	pANCA	perinuclear Anti-Neutrophil Cytoplasmic Antibodies
DDAH	Dimethylarginine Dimethylaminohydrolase	PCR	Protein/Creatinine Ratio
DKD	Diabetic Kidney Disease	PGF	Platelet-derived Growth Factor
DM	Diabetes Mellitus	PRMT	Protein arginine Methyl-Transferases
DNA	Deoxyribonucleic acid	PTH	Parathyroid Hormone
EESI-MS	Extractive Electrospray Ionization Mass Spectrometry		
eGFR	Estimated Glomerular Filtration Rate	RASS	Renin Angiotensin System
ERPF	Effective Renal Plasma Flow	RBC	Red Blood Cells
ESRD	End Stage Renal Disease	RNA	RiboNucleic Acid
FDA	Food and Drug Administration	RRT	Renal Replacement Therapy
FF	Filtration Fraction	RVR	Reno-Vascular Resistance
FGF	Fibroblast Growth Factor	SBP	Systolic Blood Pressure
FSGS	Focal Segmental Glomerulo-Sclerosis		
GBM	Glomerular Basement	SDMA	Symmetric

HbA1c	Membrane Hemoglobin A1c	SeeKD	Dimethylarginine
HF	Heart Failure	SLE	See Kidney Disease
HIV	Human Immunodeficiency Virus	SUN	Systemic Lupus Erythematosus
HUS	Hemolytic Uremic Syndrome	TA	Saliva Urea Nitrogen
I.V	Intravenous	TGF- β	Tubular Atrophy
IDA	Iron Deficiency Anemia		Transforming growth factor beta
IF	Interstitial Fibrosis	TINU	Tubulo-Interstitial Nephritis and Uveitis
IF- γ	InterFeron gamma	TTP	Thrombotic thrombocytopenic purpura
IgA	Immunoglobulin A	uNCR	Urinary Neutrophil Gelatinase-Associated Lipocalin (NGAL) to Creatinine Ratio
MRA	Magnetic Resonance Angiography	VCUG	Voiding CystoUrethroGram
NDD-CKD	Non–Dialysis- Dependent CKD	VDRL	Venereal Disease
NHANES	National Health and Nutrition Examination Survey		Research Laboratory



Abstract

Abstract

Abstract

Context: Neuropeptide Y (NPY) is a sympathetic neurotransmitter with wide-ranging effects in various organ systems, from the central nervous system (CNS) to the cardiovascular (CV) system, the bone and the renal system. There is a strong association between serum concentration of NpY and deterioration of eGFR and proteinuria as suggested by recent studies ^{1,2}, however, its real effect on chronic kidney disease (CKD) progression is uncertain.

Aim:

Assess the relationship between NpY and progression of CKD.

Settings and Design:

An observational, prospective case-control study of thirty CKD adult patients and thirty healthy control adult subjects.

Methods and Material:

All participants were conducted to renal function tests (serum creatinin, blood urea, serum Na, K, P and Ca and calculation of estimated glomerular filtration rate), complete blood count, urinary protein/creatinin ratio, serum NpY and pelvi-abdominal ultrasonography at baseline and repeated for the patients only after six months as follow up.

Statistical analysis used:

Statistical presentation and analysis of the present study was conducted, using the mean, standard deviation, student t-test, Paired t-test, Chi-square, Linear Correlation Coefficient and Analysis of variance [ANOVA] tests by SPSS V17.

Results:

The mean of serum NpY was 438.333 ± 206.850 at baseline then became 630.667 ± 264.926 after follow up. Urinary PCR ranged from 0.2- 3.1 at baseline to 0.2- 2 after six months. The patients' group mean eGFR was 36.900 ± 17.851 and became 31.373 ± 17.852 ml/min/1.73m².

Conclusion:

Serum NpY could be a useful marker that can be used as diagnostic and progression predictor for CKD.



Introduction

Introduction

Chronic kidney disease (CKD) is a term that consists of all degrees of reduced renal function, from damaged-at risk through mild, modest and severe chronic renal failure.

CKD is more prevalent in the aged population, while younger patients typically experience progressive reduction of kidney function, thirty percent of patients over sixty-five years of age with CKD have steady disease [O'Hare; et al., 2007].

The recommendations (KDOQI and KDIGO) specify CKD as either renal damage or a reduced glomerular filtration rate (GFR) of less than 60 mL/min/1.73 m² no less than 3 months. No matter the underlying aetiology, once the loss in nephrons and decrease of functional renal mass reaches a certain point; the rest of the nephrons get started out a process of permanent sclerosis that causes an intensifying fall in the GFR [Schnaper, 2014].

The brand new classification of CKD based upon 3 categories, cause (C category), GFR (G category), and albuminuria (A category), cause of CKD based on occurrence or absence of systemic disease and the location within the kidney of detected or presumed pathologic-anatomic studies. (Not Graded) [Akbari; et al., 2015].

The G category in CKD is classified as follow [Akbari; et al., 2015]:

- G1: Kidney destruction with normal or increased GFR (≥ 90 mL/min/1.73 m²).
- G2: Mild reduction in GFR (60-89 mL/min/1.73 m²).
- G3a: Moderate decrease in GFR (45-59 mL/min/1.73 m²).