EFFECT OF HEMODIALYSIS AND RENAL TRASPLANTATION ON PLASMA APELIN LEVEL IN END STAGE RENAL DISEASE PATIENTS

Thesis
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Abstract

Background: Apelin, a newly discovered adipocytokine, is produced by white adipose tissue and is also expressed in the kidney and heart. Increasing evidence suggests a role for apelin in the pathology of the cardiovascular system. Cardiovascular disease is a major contributor to the mortality and morbidity in patients with chronic renal failure. The aim of this study was to assess effect of hemodialysis and renal transplantation on plasma apelin level and to find possible correlations between apelin and echocardiographic parameters in hemodialyzed patients.

Patients and Methods: We investigated plasma apelin levels (using commercially available kits) in 40 adult subjects: a group of 15 (12 males, 3 females) hemodialyzed patients scheduled for renal transplantation (group 1), a group of 15 (11 males, 4 females) hemodialyzed patients on regular dialysis treatment for ESRD (group 2) and a group 10 (6 males, 4 females) healthy control subjects (group 3). An echocardiography was performed for all subjects.

Results: We found that plasma apelin levels are reduced in hemodialyzed patients. Plasma apelin was also found to be positively correlated with LVESD, RV and LA in our ESRD patients included in the study. Regarding the effect of

hemodialysis on plasma apelin levels we found that there is no significant effect, while levels increased two weeks after successful kidney transplantation.

Conclusions: Apelin level was significantly lower in dialyzed patients and it correlated significantly with some echocardiographic parameters in these patients, thus it might be involved in the pathophysiology of cardiovascular disease in chronic renal failure. Hemodialysis has no significant effect on plasma apelin levels, while two weeks after kidney transplantation, apelin concentrations were significantly elevated, however, they were still below normal values of healthy controls. Since apelin is an inotrope in normal and failing hearts, this finding may have clinical implications for future use of apelin as a novel inotropic agent for patients with uremic cardiomyopathy.

Key Words

Apelin _ Hemodialysis _ Transplantation_ Echocardiography

Table of contents

List of Tables

List of Figures

List of abbreviations

ACE	Angiotensin-Converting Enzyme
ACR	Albumin:Creatinine Ratio
ADH	Anti-Diuretic Hormon
ADMA	Asymmetric di-methylarginine
Ang II	Angiotensine II
ANP	Atrial Natriuretic Peptides
APJ	Adipocytokine Receptors
ARIC	Atherosclerosis Risk in Communities
AT-1	Angiotensin receptor Type 1
BMI	Body Mass Index
BNP	Brain Natriuretic Peptides
CAD	Coronary Artery Disease
CKD	Chronic Kideny Disease
CRC	Cardiorenal Connection
CRF	Chronic Renal Faliure
CRP	C-reactive protein
CVD	CardioVascular Disease
ECFV	Extra-Cellular Fluid Volume
eNOS	endothelial NO Synthase

ERK	Extracellular signal-Regulated Kinase
ESRD	End-Stage Renal Disease
GFR	Glomerular Filtration Rate
GN	Glomerulonephritis
GPCR	G protein coupled receptors
H_2O_2	Hydrogen peroxide
HD	Haemodialysis
HDL	High Density Lipoprotein
HIV	Human Immunodeficiency Virus
icv	Intracerebroventricular
IL-1ß	Inter-Leukine-1 ß
IL-6	Inter-Leukine-6
K/DOQI	Kidney Disease Outcomes Quality Initiative
KEEP	Kidney Early Evaluation Program
LDL	Low-Density Lipoprotein
LVH	Left Ventricular Hypertrophy
MHC	Major Histocompatibility Complex
MI	Myocardial Infarction
NF-$_K$B	Nuclear Factor kappa B
NO	Nitric Oxide

NOS	Nitric Oxide Synthase
NPY	Neuropeptide Y
NYHA	New York Heart Association
PAI-1	Plasminogen Activator Inhibitor-1
PDGF	Platelet-Derived Growth Factor
PI3K	Phosphat Idylinositol 3-kinase
RAS	Renin Angiotensin System
RBF	Renal blood flow
ROM	Reactive oxygen metabolites
ROS	Reactive Oxygen Species
RRT	Renal Replacement Therapy
SCRS	Severe Cardio-Renal Syndrome
SHR	Spontaneously Hypertensive Rat
SNS	Sympathatic Nervous System
SOD	Superoxide Dismutase
TGF-ß1	Transforming Growth Factor-β1
TNF_{α}	Tumour Necrosis Factor alpha
Tx	Transplantation
VLDL	Very-Low-Density Lipoprotein

Introduction and Aim of the Work

Introduction:

Apelin, a newly discovered adipocytokine, is produced by white adipose tissue and is also expressed in the heart and lung vasculature, in the kidney and in the supraortic and paraventricular nuclei (Boucher **et al., 2005).**

The family of apelin peptides is derived from a single gene and activates the 7-transmembrane G-protein coupled receptor (APJ) which was first cloned in 1993 ,orphaned for many years till the endogenous ligand, apelin, was subsequently isolated (**Tatemoto et al., 1998).**

The preprotein of 77 amino acid residues is cleaved to active peptides of 12, 13, and 36 amino acids (**Boucher et al., 2005).**The apelin system is active on the cardiovascular system (very potent positive inotrope and vasodilator), the hypothalamus (a diuretic effect through arginine vasopressin) and on the adipoinsular axis **(Foldes et al., 2003).**

Recently, the apelin-APJ system has been postulated to play an important role in cardiovascular homeostasis **(Kleinz and Davenport, 2005).** Plasma apelin levels were found to be increased in patients with early stages of heart failure and decreased in late stages of heart failure **(Chen et al., 2003).** The fact that apelin exerts the most potent positive inotropic action (among all identified inotropic agents) in normal hearts **(Szokodi et al., 2002)** suggests a role for reduced apelin levels

in the pathogenesis of heart failure. Indeed, in rat failing hearts, administration of apelin augmented pressure development and cardiac output **(Berry et al., 2004).**

Chronic renal failure can have a causative role in the progression of heart failure through the reduced clearance of cardiac toxins, alterations in fluid volume, and promotion of vascular damage through changes in blood pressure and circulating factors **(Zoccali et al., 2002).**

Kidney disease and cardiovascular disease (CVD) seem to be lethally synergistic and both approach the level of epidemic. CVD is a major contributor to the mortality and morbidity in patients with chronic renal failure. The recognition of the similarities between the pathogenesis and risk factors of CVD and chronic renal failure has led to the suggestion that they are outcomes of the same underlying disorders **(Sarnak et al., 2000).**

It has been reported that apelin is reduced in hemodialyzed patients and is related to their echocardiographic features (**Malyszko et al., 2008).**

Aim of the Work:

To investigate plasma apelin and its associations with echocardiographic parameters in hemodialyzed patients, and to study the effect of hemodialysis and renal transplantation on plasma apelin levels.

Chapter 1

Chronic kidney disease (CKD)

CKD is defined as kidney damage or glomerular filtration rate (GFR) <60 ml/min/1.73 m^2 for 3 months or more irrespective of the cause. The Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines have classified CKD into five stages:

CKD Stage	***Definition***
1	Normal or increased GFR; some evidence of kidney damage reflected by microalbuminuria/proteinuria, hematuria or histological changes.
2	Mild decrease in GFR (89-60 ml/min/1.73 m^2).
3	Moderate decrease in GFR (59-30 ml/min/1.73 m^2).
4	Severe decrease in GFR (29-15 ml/min/1.73m^2).
5	GFR < 15 ml/min/1.73 m^2; when renal replacement therapy in the form of dialysis or transplantation has to be considered to sustain life.

(American Journal of Kidney Disease, 2002)

EPIDEMIOLOGY OF ESRD

In the UK, the incidence of ESRD treated by renal replacement therapy (RRT) is around 100 new patients per million population (pmp)/year; this has doubled over the past decade and is expected to continue to rise by 5-8% annually but remains well below the European average (~129pmp) and that of the USA (333 pmp) **(U.S.Renal Data System, 2004).**

The rise in ESRD patients worldwide most likely reflects aging of the population (annual incidence of ESRD in the population over 65 years in the UK > 350pmp, USA >1200pmp), and the global epidemic of type 2 diabetes mellitus. It is predicted that the number of diabetics worldwide (currently ~154 million) will double within the next 20 years with the highest increase in the developing world. In addition, increasing access to RRT worldwide has encouraged the referral and treatment of patients who, in the past, were denying RRT**. (U.S.Renal Data System, 2004)**

SCREENING FOR CKD

In order to decrease the growing tide of CKD, early detection and management is advocated. This is often initiated by simple dipstick analysis of the urine. Whole population screening is not cost-effective. A more realistic approach would be to screen populations at high risk such as the elderly, obese, diabetic and hypertensive individuals, high-risk communities