KASR ALAINY

Study of Plasma Long Pentraxin 3 (PTX3) as a Marker of Endothelial Dysfunction in Type 2 Diabetes Mellitus

THESIS

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Elham Mohamed Yousief

Abstract

Albuminuria and inflammation predict cardiovascular events. Pentraxin 3, an inflammatory mediator produced by endothelial cells, may have a role in atherogenesis.

Our study was conducted on 50 patients with type 2 diabetes mellitus classified into two groups: group I which included 25 type 2 diabetes patients with normal UAE and group II included 25 patients with type 2 diabetes with microalbuminuria and 20 healthy volunteers as a control group. We aimed to measure plasma levels of long pentraxin 3 (PTX3) in patients with type 2 DM with and without microalbuminuria with normal renal function and without overt cardiovascular disease and to evaluate its utility in the early detection of endothelial dysfunction compared to other known markers of endothelial dysfunction (vWF activity and flow dependent arterial dilatation).

We found that type 2 diabetic patients with microalbuminuria and normal GFR (stage 1 CKD) have significantly higher PTX-3 concentrations and significantly lower flow mediated dilatation (FMD) than normal individuals and diabetics with normal UAE and normal kidney functions also vWF activity are significantly higher in patients with type 2 diabetes with normal UAER (group I) and in patients with microalbuminuria (group II) compared to controls. There was a significant positive correlation between PTX3 and vWF activity, duration of diabetes, fasting glucose, HbA1c, cholesterol and triglyceride and a significant negative correlation between PTX3 and FMD in all diabetic patients.

Conclusion: Our study suggests a link among albuminuria, markers of ED, and development of atherosclerotic complications through pathways that may involve PTX3.

Key words: (Endothelial dysfunction, type 2 diabetes, long pentraxin 3)

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List of Abbreviations

AACE	American association of clinical endocrinologist
ABI	Ankle brachial index
ACCF	American College of Cardiology Foundation
ACCORD	Action to Control Cardiovascular Risk in Diabetes)
ACE	Angiotensin converting enzyme
ACSs	Acute coronary syndromes
ADA	American diabetes association
ADMA	Asymmetric dimethylarginine
ADVANCE	Action in Diabetes and Vascular Disease
ADP	Adenosine di-phosphate
AECAs	Anti-endothelial cell antibodies
AGEs	Advanced glycation end products
AMP	Adenosine mono-phosphate
AP-1	Activator protein-1
AR	Aldose reductase
ARBs	Angiotensin receptor blockers
APS	Antiphospholipid syndrome
ARBs	Angiotensin receptor blockers
ATT	Anti-thrombotic Trialists'
BH4	Tetrahydrobiopterin
BCG	Bacille Calmette-Guerin
BMI	Body mass index
CAD	Coronary artery disease
CHD	Chronic heart disease
c-GMP	cyclic Guanosine monophosphate
cIMT	Carotid intima media thickness

CKD	chronic kidney disease
CNS	Central nervous system
CRP	C-reactive protein
CSF	Colony stimulating factor
CV	Cardiovascular
CVD	Cardiovascular disease
DAG	Diacylglycerol
DCs	Dendritic cells
DCCT	Diabetes Control and Complications
DM	Diabetes mellitus
DPN	Diabetic peripheral neuropathy
DRS	Diabetic Retinopathy Study
dsDNA	Double stranded DNA
eCcr	Estimated creatinine clearance
EDHF	Endothelium-derived hyperpolarizing factor
ED-FMD	Endothelial dependent flow-mediated vascular dilation
ED	Endothelial dysfunction
ELISA	Enzyme linked immune sorbent assay
eNOS	Endothelial NOS
EPCR	Endothelial protein C receptor
EPCs	Endothelial progenitor cells
ETDRS	Early Treatment Diabetic Retinopathy Study
ESRD	End-stage renal disease
ET	Endothelin
FBS	Fasting blood sugar
FDA	Food and Drug Administration
FFA	FFA
FMD	Flow mediated dilatation

GAP	Glyceraldehydes-3-phosphate
GFR	Glomerular filtration rate
GLUT	Glucose transporters
GTN	Nitroglycerin
GTP	Guanosine triphosphate
H2O2	Hydrogen peroxide
HDL	High density lipoprotein
HDLC	High density lipoprotein cholestrol
HbA1c	Glycosylated haemglobin
HRP	Horse radish peroxidase
HUVEC	Human umbilical vein endothelial cells
ICAM-1	Intercellular adhesion molecule-1
ICH	Intracranial hemorrhage
IGM	Impaired glucose metabolism
IGT	Impaired glucose tolerance
IL	Interleukin
IMT	Intima media thickness
iNOS	Inducible or inflammatory NOS
INVEST	International Verapamil SR-Trandolapril
IKB	Inhibitor of kappa B
IR	Insulin resistance
IRD	Inflammatory rheumatic disease
IS	Insulin-sensitive
LDL	Low density lipoprotein
LADA	Latent autoimmune diabetes in adults
LFA-1	Leucocyte function associated antigen-1
LOPS	Loss of proprioceptive sensations
LP	Lipid peroxidation

LPS	Lipopolysaccharide
MAP	Mitogen activated protein
MBF	Myocardial blood flow
MCP-1	Monocyte chemotactic protein-1
MI	Myocardial infarction
MCTD	Mixed connective tissue disease
MDRD	Modification of Diet in Renal Disease
MoDC	Monocytes DC
MODY	Maturity-onset diabetes of the young
MPO	Myeloperoxidase
MyDC	Myeloid DC
NADPH	Nicotinamide adenine dinucleotide
NCEP	National Cholesterol Education Panel
NFkB	Nuclear factor kappa B
NGT	Normal glucose tolerance
NHANES	National Health and Nutrition Examination Surveys
NK	Natural killer Cells
NO	Nitric oxide
NOS	Nitric oxide synthase
nNOS	Neuronal NOS
nRNP	Ribonucleoproteins
O.D.	Optical density
OGTT	Oral glucose tolerance test
PAD	Peripheral arterial disease
PAF	Platelet activating factor
PAH	Pulmonary arterial hypertension
PAI-1	Plasminogen activator inhibitor-1
PARP	Activation of poly (ADP-ribose) polymerase

PBMCs	Peripheral bone marrow cells
pDC	Plasmoid DC
PIP3	Phosphatidylinositol triphosphate 3
PKC	Protein kinase C
PTX3	Long pentraxin 3
RA	Rheumatoid arthritis
RAS	Renin-angiotensin system
ROS	Reactivee oxygen species
SAP	Serum amyloid P component
SDH	Sorbitol dehydrogenase
sICAM-1	Soluble intercellular adhesion molecule-1
SLE	Systemic lupus erythomatouses
SSc	Systemic sclerosis
SPECT	Single photon emission computed tomography
STIMS	The Swedish Ticlopidine MulticenterStudy
sTNFR-I	Soluble TNF receptor I
sVCAM-1	Soluble vascular cell adhesion molecule-1
TCAs	Tricyclic antidepressants
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TMB	Tetra methyl benzidine
TFPI	Tissue factor pathway inhibitor
TIA	Transient ischemic attack
TLR	Toll-like receptors
TM	Thrombomodulin
TNFa	Tumour necrosis factor a
TSG	TNF-stimulated genes
tPA	Tissuee plasminogen activator

UAE	Urinary albumin excretion
U1 RNP	U_1 ribonucleoprotein
UKPDS	UK prospective diabetes study
VCAM	Vascular cell adhesion molecule
VEGF	Vascular endothelial growth factor
VLA-4	Very late antigen-4
vWF	von Willebrand factor
vWFAg	Von Willebrand factor antigen
WHO	World of health and organization

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Introduction

One of the earliest clinically detectable abnormalities in diabetic nephropathy is microalbuminuria that eventually progresses to albuminuria and overt nephropathy. Albuminuria is viewed as a marker of glomerular disease and is nowadays recognized as a strong and independent predictor of cardiovascular disease (CVD) risk among individuals with and without diabetes, independent of other recognized risk determinants, including reduced glomerular filtration rate (GFR) ***(Stehouwer and Smulders, 2006).*** Although the nature of the link between urinary albumin excretion (UAE) and cardiovascular risk still remains poorly understood, common pathophysiologic processes may contribute, such as endothelial dysfunction (ED) and/or chronic low grade inflammation ***(Stehouwer and Smulders., 2006).*** In fact, increased UAE is considered to indicate ED ***(Stehouwer et al., 2004).*** At the same time, UAE has been associated with plasma inflammatory mediators ***(Abrahamian et al., 2007).***

Long pentraxin 3 (PTX3) is a multimeric inflammatory mediator that is structurally linked to short pentraxins, such as C-reactive protein (CRP) and serum amyloid P component ***(Mantovani et al., 2008).*** PTX3 is produced by a variety of tissues and cells, including vascular endothelial cells and macrophages ***(Mantovani et al., 2006).*** Because of its extrahepatic synthesis (in contrast to CRP), the PTX3 level is believed to be a true independent indicator of disease activity because PTX3 is produced at sites of inflammation and is intimately linked to ED ***(Fazzini et al., 2001).*** PTX3 levels are elevated in patients with chronic kidney disease (CKD) ***(Boehme et al., 2007)*** and represent a novel mortality risk

factor in stage 5 CKD, independent of traditional risk factors and CRP itself ***(Tong et al.,2007).*** A strong associations was observed between PTX3 and markers of ED, such as soluble vascular cellular adhesion molecule-1 (VCAM-1) and fibrinogen, in patients with chronic kidney disease had ***(Tong et al., 2007)*** led to hypothesis that PTX3 may link albuminuria with ED and, ultimately, atherothrombotic complications.

Background:

Albuminuria and inflammation predict cardiovascular events. Pentraxin 3, an inflammatory mediator produced by endothelial cells, may have a role in atherogenesis.

Aim of the Study

The aim of this study is to measure plasma levels of long pentraxin 3 in patients with type 2 DM with and without microalbuminuria (without clinical cardiovascular disease) and to find its relationship to other known markers of endothelial dysfunction (vWF activity and flow dependent arterial dilatation), degree of glycemic control.