ENDOTHELIAL DYSFUNCTION IN CHRONIC KIDNEY DISEASE

Essay

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Internal Medicine

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List of Abbreviations

ACE	→	Angiotensine converting enzyme
Ach	→	Acetylcholine
ADMA	→	Asymmetric dimethylarginine
AGEs	→	Advanced glycosylation end products
AII	→	Angiotensin-II
BH4	→	Tetrahydrobiopterin
CAMs	→	Cellular adhesion molecules
CECs	→	Circulating endothelial cells
cGMP	→	cyclic Guanosine monophosphate
CKD	→	Chronic kidney disease
CRF	→	Chronic renal failure
CRP	→	C-reactive protein
CVD	→	Cardiovascular disease
DDAH	→	Dimethylarginine dimethylaminohydrolases
EC activation	→	Endothelial cell activation
ECD	→	Endothelial cell dysfunction
EDHF	→	Endothelial-derived hyperpolarising factor

EFF	→	Effective filtration fraction
eNOS	→	Endothelial nitric oxide synthase
EPC	→	Endothelial progenitor cells
E-Selectin	→	Endothelial selectin
ESRD	→	End-stage renal disease
ET-1	→	Endothelin-1
ETA	→	Endothelin receptor type A
ETB	→	Endothelin receptor type B
FMD	→	Flow mediated vasodilatation
GBM	→	Glomerular basement membrane
GCH1	→	Guanosine 5'-triphosphate cyclohydrolase 1
GFR	→	Glomerular filtration rate
GTPcH1	→	GTP cyclohydrolase 1
HMG-CoA	→	3-hydroxy-3-methylglutaryl-coenzyme A
ICAM	→	Intercellular adhesion molecules
I-kB	→	Inhibitor kappa-B
IL	→	Interleukin
IR	→	Insulin resistance
LDL	→	Low density lipoprotein

LDL-C	→	Low-density lipoprotein cholesterol
L-NMMA	→	NG-monomethyl-L-arginine
LOX-1	→	Lectin-like oxidized LDL receptor-1
MCP-1	→	Macrophage chemoattractant peptide-1
MMP	→	matrix metalloproteinases
MPO	→	Myeloperoxidase
NADH	→	Nicotinamide adenine dinucleotide
NADPH	→	Nicotinamide adenine dinucleotide phosphate
NF-1	→	Neurofibromatosis type1
NFkB	→	Nuclear factor kappa-B
NF-kB	→	Nuclear factor k of B cells
NIH	→	National Institutes of Health
NO	→	Nitric oxide
NOS	→	Nitric oxide synthases
PAI	→	Plasminogen activating inhibitor
PAT	→	Peripheral arterial tonometry
PETN	→	Pentaerythritol tetranitrate

PRMTs → Protein arginine methyltransferases

RBF → Renal blood flow

ROS → Reactive oxygen species

SDMA → Symmetric dimethylarginine

TNF-α → Tumor necrosis factor-α

T-PA → Tissue plasminogen activator

VCAM → Vascular cellular adhesion molecules

VSMC → Vascular smooth muscle cell

Vwf → vonWillebrand Factor

XO → Xanthine oxidase

Introduction

The endothelium is a thin monocelular layer that covers all the inner surface of the blood vessels, separating the circulating blood from the tissues. It has been considered an active biologic interface between the blood and all other tissues. The single layer of continuous endothelium lining arteries and veins forms a unique thromboresistant layer between blood and potentially thrombogenic subendothelial tissues ***(Esper, et al., 2006).***

It works as a receptor-effector organ and responds to each physical or chemical stimulus with the release of the correct substance with which it may maintain vasomotor balance and vascular-tissue homeostasis ***(Esper, et al., 2006).***

Chronic kidney disease (CKD) is a worldwide public health problem and is associated with a high prevalence of cardiovascular disease (CVD). The epidemiologic association between CKD and CVD has been firmly established. Traditional CVD risk factors such as hypertension, age, lifestyle, diabetes mellitus and hyperlipidemia do not fully explain the high prevalence of CVD in CKD ***(Linden, et al. 2008) .***

Several nontraditional CVD risk factors so-called novel risk factors, such as endothelial dysfunction, oxidative stress and sympathetic over activation are highly prevalent in these patients and seem to play a far more important role for vascular

disease than in the general population . Indeed, several biochemical markers of ED and inflammatory activity have been shown to be independent risk factors of cardiovascular morbidity and mortality in CKD patients ***(Linden, et al. 2008) .***

Endothelial dysfunction is recognized as a key process in acute and CRF as well as ESRD of all causes. Endothelial activation plays a central role in hemolytic uremic syndrome, various types of glomerulonephritis, hypertension, metabolic syndrome, and diabetic renal disease ***(Mark, et al., 2006).***

Glomerular endothelial injury is an early event in various renal diseases, including glomerulonephritides , vasculitides, thrombotic microangiopathies and renal transplant rejection and is viewed as a crucial factor in the progression of renal disease, regardless of the initial cause. Even more interesting, detached circulating endothelial cells including inflammatory endothelial cells and endothelial progenitor cells (EPC) may serve as potential markers of endothelial damage in CKD ***(Stenvinkel, et al. 2008) .***

An imbalance between the expression of circulating endothelial cells and EPC seems to exist in CKD. This imbalance may contribute to the pathogenesis and progression of the atherosclerosis process in CKD patients and may be linked to the ability of circulating inflammatory endothelial cells to interfere with the functional capacity for vessel wall repair by EPCs ***(Stenvinkel, et al. 2008) .***

The usual parameter assessed when testing endothelial function is endothelium-dependent vasodilation, which can be

assessed by doppler flow measurements, brachial artery ultrasound imaging, fingertip pulse pressure tonometry, measurement of intima-media thickness ***(Dierk, et al. 2004).***

The central role of the endothelium in the development of CVD has led to the search for novel and biologically relevant biochemical markers to estimate endothelial function and injury. So several markers of ED can be assessed in plasma, such as asymmetric dimethylarginine (ADMA), soluble vascular cell adhesion molecule-1 (sVCAM-1), von Willebrand factor (vWf), microalbuminuria, E-selectin, CD40 ligand, and lectin-like oxidized LDL receptor-1 (LOX-1) ***(Stenvinkel, et al. 2008) .***

Treatment of the underlying disease may restore endothelial function. In patients with chronic renal failure, renal transplantation restores renal function and may improve ED ***(Barac, et al. 2007) .***

EPCs promote neovascularization and endothelial repair. It is likely that restoration of the angiogenic cascade by autologous EPCs involved not only generation of new vessels but also acceleration of their maturation and stabilization. This contributed to preserving the blood supply, hemodynamics, and function of the kidney, supporting EPCs as a promising therapeutic intervention for preserving the kidney in renovascular disease ***(Chade , et al. 2009).***

Aim of the work

The aims of the present essay are :

1-To highlight the pathophysiological mechanisms, effects and importance of ED in CKD patients .

2- To review potential novel markers and different methods of assessment of ED .

3- To clarify recent advances in the treatment of ED .

The Endothelium

Anatomy & physiological aspects

The human body contains approximately 10^{13} endothelial cells , weighing approximately 1 kg, and covering a surface area of 4000 to 7000 square meters . Endothelial cells form the inner lining of all blood vessels within the vascular tree (eg : endocardium, arteries, arterioles, capillaries, venules, and veins) ***(Wagner, et al., 2008)***.

Vascular endothelial cells form a single layer of simple squamous lining cells. The cells themselves are polygonal in shape, varying between 10 and 50 μm in diameter, and elongated in the long axis, orienting the cellular longitudinal dimension in the direction of blood flow. The endothelial cell has three surfaces: nonthrombogenic (luminal), adhesive (subluminal) and Cohesive ***(Yang, et al., 2000)***.

The luminal surface is smooth and devoid of electron-dense connective tissue. The luminal membrane or glycocalyx adds significantly to the vessel's thromboresistant properties, carrying a negative charge that repels similarly charged circulating blood cells ***(Yang, et al., 2000)***.

The subluminal (abluminal) surface adheres to connective tissue within the subendothelial zone. Small processes penetrate through a series of internal layers to form myoendothelial junctions with subjacent smooth muscle cells***(Yang, et al., 2000)***.