**Invited Editorial**

**Title: Endothelial cell and Vascular Smooth Muscle Cell dysfunction in Chronic Kidney Disease**

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Healthy existence of individual human cells is dependent on adequate supply of nutrients and removal of waste products, which is maintained by an intricate network of capillaries and blood vessels. The endothelial cells, which forms the inner lining of all capillaries and blood vessels possess amazing properties for establishing and controlling of the flow of nutrients and waste products in the tissues microenvironment, by angiogenesis and autoregulation [1]. The vascular smooth muscle cells (VSMC), with their ability to change shape dramatically on external stimuli, can constrict and dilate blood vessels to decrease and increase flow in the blood vessel. In collaboration with the endothelial cells, VSMC mediates the acute and chronic changes in tissue perfusion in response to short and long term alteration in function of tissues, under physiological and pathological conditions [2].

Several biological molecules, some transported by the blood and the laminar blood flow, regulate physiological function of the endothelium. In response, the endothelial cells release biological molecules to carry out the necessary functions such as vasodilatation, platelet inhibition and anticoagulation. When stimulated by inflammatory cytokines, complements, bacterial products, lipids and reactive oxygen species the endothelial cells respond by releasing mediators to cause vasoconstriction, platelet aggregation, thrombosis and atherosclerosis [2]. The cross talk between endothelial cells and VSMC, a very important mechanism to maintain appropriate blood flow in health and disease, involve vasodilator substances such as nitric oxide, oestrogen etc.; and vasoconstrictor substances such as endothelin 1 (ET1), angiotensin II and catecholamine. The migratory and proliferative activities of the VAMC are up-regulated by platelet derived growth factor (PDGF), thrombin, fibroblast growth factor (FGF), interferon γ (IFNγ), interleukin 1 (IL1), endothelin 1 (ET1) and down-regulated by tumour growth factor β (TGFβ) and heparin (figure 1).

In patients with chronic kidney disease (CKD) both endothelial and VSMC are affected, as evidenced by abnormal brachial artery flow mediated dilatation (FMD) and non-endothelial dependent, nitroglycerine-induced vasodilatation (NID) [3]. FMD and NID have shown to predict adverse outcome in other populations [4,5]. In the study published in this issue of the journal by Iwomoto et al. both FMD and NID were worse in CKD patients compared to non-CKD patients. The cause of abnormal FMD in CKD patients can be related to inflammation and oxidative stress as suggested by the relationship between white cell count and FMD in the present study. The cause of abnormal NID can be endothelial dysfunction or inflammation in CKD patients, but the aetiology is not clear from the present study. Previous intervention studies have shown simultaneous improvement of FMD and NMD in CKD patients suggesting but not proving the effect of endothelium on VSMC function in CKD patients [6].

In the study by Iwomoto et. Al. CKD was independently associated with NID after adjustment with age, hypertension, diabetes, smoking and cardiovascular disease. This strongly suggest a possible adverse impact of kidney failure on VSMC function. The impact of CKD may be mediated by the above mentioned VSMC growth and migration inducing substances. The long term effects of such VSMC dysfunction can be as follows. The dysfunctional VSMC may migrate towards intima and cause intimal hyperplasia [7].The VSMC dysfunction may cause deposition of abnormal extracellular matrix, stiffening of arteries, high pulse pressure and associated morbidity and mortality [8]. CKD induced VSMC dedifferentiation can cause vascular calcification a major mortality in all CKD patients [9]. The stimulated VSMC in CKD patients are also important contributors of atherosclerosis causing myocardial infarctions and stroke.

Diabetes is a common cause of and coexisting condition in patients of CKD, which is independently associated with abnormal endothelial cell and VSMC dysfunction. In the study by Iwamoto et al. the effect of CKD on NID were independent of presence of diabetes and was similarly affected in CKD patients with or without CKD. The prevalence of VSMC dysfunction was worse in diabetics for all GFR stages compared to non-diabetics. These observations suggest an independent and additive effect of CKD on VAMC dysfunction over and above diabetes.

The lack of independent correlation of CKD with FMD in the reported study is intriguing. The authors suggest that endothelial dysfunction happens in early CKD and not in advanced CKD. This is contrary to the demonstration of abnormal FMD in CKD cohorts in previous studies including patients with end stage kidney disease and on dialysis [3]. The authors also suggest that that pre-existing CV risk factors cause abnormal FMD and CKD does not cause additional abnormality; as suggested by their findings that endothelial dysfunction in diabetes, defined as FMD in the lowest quartile was similar in patients with CKD than without CKD. However this is also contrary to what have been demonstrated in other cohorts [10]. The lack of correlation needs better explanation and further verification in larger well characterised populations. The changes in FMD and NMD with progressive CKD may also help resolve this issue.

Thus vascular smooth muscle cell dysfunction is an important surrogate marker of vascular dysfunction in CKD patients, similar to endothelial dysfunction and future studies should endeavour to investigate the exact nature of VSMC dysfunction and possible interventions for improvement.

**Figure 1**

Title: Endothelial cell and vascular smooth muscle cell, abnormalities in CKD

Legend: Figure showing the mediators affecting the function of endothelial and vascular smooth muscle. The mediators causing abnormalities in CKD are shown at the bottom of the figure.

NO=nitric oxide, endothelin 1 = ET1, angiotensin II = AngII, platelet derived growth factor =PDGF, fibroblast growth factor= FGF, interferon γ = IFNgamma, interleukin 1= IL1, endothelin 1=ET1, tumour growth factor β =TGFβeta, Vascular endothelial growth factor=VEGF, Epinephrine=Epi, Non Epinephrien=Nor Epi, von Wllibrand factor=vWF, Asymmetric dimethylarginine=ADMA, Colony stimulating factor=CSF, Tumour necrosis factor α=TNFalpha

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**Figure 1**

