The dysfunctional endothelium in CKD and in cardiovascular disease: mapping the origin(s) of cardiovascular problems in CKD and of kidney disease in cardiovascular conditions for a research agenda

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Endothelial dysfunction resulting in disintegration of vascular structure and function is a key element in the progression of chronic kidney disease (CKD). Many risk factors—traditional and non-traditional—are thought to have a role in the progression and development of cardiovascular disease (CVD) in patients with CKD. However, many risk factors await definitive confirmation of their clinical relevance obtained from intervention trials. Moreover, the investigation of the relative contribution of these factors to the twin-risk problem of CVD and progression in patients with CKD is one of the most important future challenges for nephrologists.

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The endothelium is the innermost (single) cell lining of all blood vessels within the body; however, endothelial cell phenotypes may vary considerably in structure and function within different vascular regions.[1,2] For example, even between glomerular and peritubular capillaries, endothelial function differs significantly because of their high specialization. In this respect, the integrity of the endothelial cell layer has a pivotal role in many aspects of vascular function, for example, control of vasomotor tone and permeability, the latter being of paramount importance particularly for glomerular capillaries. However, despite the functional diversity of endothelial cells in different vascular compartments, a key common feature is their ability to synthesize and secrete a variety of factors impinging upon vascular tone and on vascular protection.[3]

The endothelium produces a range of vasorelaxant factors, the most significant and well characterized of which is nitric oxide (NO). NO is a fundamental gas that stimulates relaxation of vascular smooth muscle cells and inhibits their proliferation, and prevents leukocyte attachment and migration into the arterial wall, and platelet adhesion and aggregation to the endothelium. Prostacyclin and

endothelium-derived hyperpolarizing factor are also important endothelium-derived vasorelaxants, with the latter contributing to endothelium-dependent vasodilatation in resistant arteries. The vast majority of studies on endothelial dysfunction have concentrated on the mechanisms responsible for the decreased bioavailability of NO, which may result from a decrease in NO production, from a decrease in activation of guanylyl cyclase, and/or from an increase in NO degradation. A decrease in NO production may result from reduced availability of substrates and cofactors for NO synthases, such as L-arginine or tetrahydrobiopterin; from a decreased expression of endothelial NO synthase (eNOS) or from a decreased activation of eNOS, such as phosphorylation of the enzyme or interactions with proteins (for example, heat shock protein 90 or calmodulin); or from high levels of endogenous inhibitors of eNOS, such as asymmetric dimethylarginine in particular. Finally, reduced NO bioavailability levels may be caused by the binding of NO to hemoglobin or from oxidative stress, which gives rise to peroxynitrite, a vasculotoxic substance. On the other hand, endothelial cells produce several vasoconstrictors, including endothelin-1, cyclooxygenase-derived prostanoids, reactive oxygen species, dinucleotide uridine adenosine tetraphosphate, and angiotensin II. When the balance between endothelium-derived vasorelaxants and vasoconstrictors is altered, endothelial dysfunction ensues.

Because of its enormous surface area within the body, the endothelium has an important role in major diseases such as hypertension and diabetes. In these conditions, the endothelium undergoes functional and structural alterations, eventually resulting in loss of its role as a protective barrier. Endothelial dysfunction is the earliest—merely functional—step in the cascade of events leading to atherosclerosis, and the fundamental feature of this condition is impaired NO bioavailability.[4,5] If perpetuated long enough, dysfunction of endothelial cells is followed by their apoptosis, which can finally result in functional and structural disintegration of the endothelial cell layer. This is paralleled by vascular 'microinflammation' as a result of leukocyte and thrombocyte activation and adhesion, which further accelerates the vessel wall damage.[6] This process leads to progressive atherosclerotic disease in larger vessels and/or complete disruption of smaller (tissue) blood vessels. Finally, vessel disappearance ('vascular rarefaction') may terminate in malperfusion and hypoxia of tissues and whole organs. For this reason, hypertension and diabetes are recognized not only as main (cardio) vascular risk factors resulting in death due to atherosclerotic complications but also as the most important conditions leading to end-stage kidney disease as a consequence of progressive glomerulosclerosis and rarefaction of postglomerular capillaries. Here, the kidney pays the definite price for its generous vascular supply as the organ with the largest total endothelial surface area.

In patients with chronic kidney disease (CKD), endothelial dysfunction may have a dual role. On the one hand, it is a crucial step in the development of cardiovascular disease (CVD). On the other hand, activation, dysfunction, and disintegration of endothelial cells in glomerular capillaries and particularly in the capillaries that nurture the renal medulla pave the way for CKD progression. It has become clear from experimental studies that vascular rarefaction in this capillary system is a crucial step toward renal tissue hypoxia and kidney damage.[7] A myriad of factors are thought to be involved in the process of endothelial dysfunction and disintegration, which, through further steps of vascular injury, finally results in end-stage CVD and/or CKD. However, the competing twin risk of patients with CKD—development of CVD and/or CKD progression—is not well elucidated. In other words, we do not understand yet why some patients progress to end-stage kidney disease without significant cardiovascular events, whereas others die before reaching terminal renal failure due to complications of severe (larger-vessel) atherosclerosis. Furthermore, in patients without CKD, a large body of evidence supports the hypothesis that endothelial dysfunction and microinflammation represent major promoters for atherosclerosis and independently predict the risk of future cardiovascular events,[8–10] whereas in patients with CKD firm evidence for this relationship has not been provided so far. Finally, the relationship between endothelial dysfunction of peripheral and renal vessels in CKD patients has not been explored in detail, and the prognostic value of endothelial dysfunction in the renal circulation for CKD progression is almost unknown. Here, the assessment of endothelial dysfunction is mostly restricted to functional tests such as the response of the renal (micro)circulation to vasodilator and/or vasoconstrictor stimuli, for example, NO inhibitors or angiotensin II—usually assessed by a change in the para-aminohippurate clearance. Furthermore, although the number of studies focusing on NO bioavailability and disturbed NO vasoregulation in CKD is on the rise, we still lack studies looking at the balance between vasorelaxant and vasoconstrictor factors rather than on single-factor perturbation.

Many risk factors—traditional and non-traditional—are thought to have a more or less important role in the development of CVD and progression in CKD patients (Table 1). Some of these are established cardiovascular risk factors, for example, hypertension and smoking, and their successful treatment or cessation results in reduced cardiovascular events and in slowing down progression. Others only seem to identify patients at risk, that is, they are only markers of risk, such as high serum homocysteine. In patients with progressive CKD, the issue is further complicated because of the appearance of uremia-specific risk factors with the potential of contributing to endothelial and vascular dysfunction and damage (Table 2). In this respect, many novel putative 'biomarkers' of risk—either for CVD or for progression—have been discovered in the last two decades. However, for many of them causality has not been proven yet, even in experimental studies, and for almost all of them the definitive confirmation of their pathophysiological role and clinical relevance from intervention trials in CKD patients is

Table 1 | Risk factors and putative 'biomarkers' for cardiovascular disease and progression in patients with chronic kidney disease

Traditional
Age
Gender (male)
Family history (genetic background)
High blood pressure
Obesity/physical inactivity
Hyper- and dyslipidemia
Increased fibrinogen/other coagulation disorders
Hyperinsulinemia
Glucose intolerance/hyperglycemia/diabetes
Smoking
?
Non-traditional
Albuminuria/proteinuria
Increased homocysteine
Increased asymmetric dimethylarginine and other endogenous nitric oxide inhibitors
Increased high-sensitivity C-reactive protein and other inflammatory markers
Increased adhesion molecules
Oxidative stress/increased production of reactive oxygen species
Increased fatty acids/high lipoprotein a
Increased advanced glycation endproducts
Reduced adiponectin and/or increased leptin
Reduced vitamin D
Increased natriuretic peptides (e.g., NT-proBNP)
?

Table 2 | CKD-specific risk factors and putative 'biomarkers' for cardiovascular disease and for progression in patients with CKD

Volume overload/increased natriuretic peptides (e.g., NT-proBNP)
Proteinuria
Increased parathormone and calcium/phosphate product
Increased fibroblast growth factor 23
Reduced vitamin D
Acidosis
Anemia
Hypoalbuminemia
Reduced fetuin A and other inhibitors of calcification
Increased asymmetric dimethylarginine and other endogenous NO inhibitors
Increased high-sensitivity C-reactive protein and other inflammatory markers
Oxidative stress/increased production of reactive oxygen species
Increased susceptibility to infections
?

Abbreviations: CKD, chronic kidney disease; NO, nitric oxide.
Some of these factors are present also in patients without CKD, but they accumulate/disperse significantly with declining kidney function.

still pending. This will certainly be one of the most important future challenges in the field of (cardio)vascular research in nephrology (Figure 1). In addition, the relative contribution of these (risk) factors and markers to the twin risk of CVD and progression in CKD patients has not been appropriately investigated so far. In the face of the many discovered putative risk factors and markers in recent years, the above questions may be of greater importance than the search for further biomarkers with uncertain significance for CVD and progression in patients with CKD.

- Definition of endothelial dysfunction of the renal (micro)circulation.
- Studying the relationship between peripheral and renal endothelial dysfunction in patients with chronic kidney disease (CKD) across the whole range of renal function and taking into account proteinuria and the nature of kidney disease.
- Testing the association of some CKD-specific factors such as low vitamin D levels and metabolic acidosis with endothelial dysfunction; performing intervention studies to explore whether these links are causal in nature.
- Testing the predictive power of peripheral and renal endothelial dysfunction for future cardiovascular events and for progression in patients with CKD.
- Characterization of risk factors versus risk markers for endothelial dysfunction and validation of risk factors for future events in intervention trials.
- Clarification of the relative contribution of risk factors for cardiovascular disease versus renal disease progression in patients with CKD.
- Validation of risk markers with respect to their ability to identify individuals at risk.
- Identification of novel risk factors and markers for cardiovascular disease and for progression in patients with CKD.
- Studying endothelial function in patients with CKD and patients with cardiovascular diseases by considering the balance of vasoconstrictors and vasodilators made up by the endothelium.

Figure 1 | Some open questions on the role of endothelium in the cardio-renal connection.

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