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

Danilo Fliser1, Andrzej Wiecek2, Gultekin Suleymanlar3, Alberto Ortiz4, Ziad Massy5,6, Bengt Lindholm7, Alberto Martinez-Castelao8, Rajiv Agarwal9, Kitty J. Jager10, Friedo W. Dekker11, Peter J. Blankestijn12, David Goldsmith13, Adrian Covic14, Gerard London15 and Carmine Zoccali16, EUropean REnal and CArdiovascular Medicine working group of the European Renal Association–European Dialysis and Transplant Association (ERA–EDTA)

1Department of Internal Medicine IV, Saarland University Medical Centre, Homburg/Saar, Germany; 2Department of Nephrology, Endocrinology and Metabolic Diseases, Medical University of Silesia, Katowice, Poland; 3Nephrology Division, Department of Medicine, Akdeniz University Medical School, Antalya, Turkey; 4IIS-Fundación Jiménez Díaz, Universidad Autónoma de Madrid, Fundación Renal Irígo Alvarez de Toledo, Madrid, Spain; 5INSERM ERI-12 (EA 4292), Amiens, France; 6Amiens University Hospital and the Jules Verne University of Picardie, Amiens, France; 7Divisions of Renal Medicine and Baxter Novum, Department of Clinical Science, Intervention and Technology, Karolinska Institutet, Stockholm, Sweden; 8Hospital Universitario de Bellvitge, IDIBELL, L’Hospitalet de Llobregat, Barcelona, Spain; 9Indiana University and VAMC, Indianapolis, Indiana, USA; 10ERA-EDTA Registry, Department of Medical Informatics, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands; 11Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, The Netherlands; 12Department of Nephrology, University Medical Center, Utrecht, The Netherlands; 13Renal Unit, Guy’s and St Thomas’ NHS Foundation Hospital, King’s Health Partners, London, UK; 14Clinic of Nephrology, C.I. Parhon University Hospital, Gr. T. Popa University of Medicine and Pharmacy, Iasi, Romania; 15INSERM U970, Hôpital Européen Georges Pompidou, Paris, France and 16Nephrology, Dialysis and Transplantation Unit and CNR-IBIM Clinical Epidemiology and Pathophysiology of Renal Diseases and Hypertension, Reggio Calabria, Italy

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 vasmotor 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

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.

Kidney International Supplements (2011) 1, 6–9; doi:10.1038/kisup.2011.6

KEYWORDS: biomarkers; cardiovascular disease; chronic kidney disease; endothelium

TO CITE THIS ARTICLE:
Fliser D, Wiecek A, Suleymanlar G et al. 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. Kidney Int Sup 2011; 1: 6-9.
endothelium-derived hyperpolarizing factor are also important endothelium-derived vasorelaxants, with the latter contributing to endothelial-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 result in loss of its role as a protective barrier. Endothelial dysfunction ensues.

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 |
| Alcohol intake |
| ? |

| 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 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.

DISCLOSURE
AC has received consulting fees from Abbott Laboratories and received lecture fees from F. Hoffmann-La Roche, Amgen, and Fresenius Medical Care Holdings. AM-C has received consulting fees from Abbott Laboratories, Roche Spain, and Abbott Spain. AO has received grant support from the Spanish Government. AW has received lecture fees from Amgen, F. Hoffmann-La Roche, and Janssen-Cilag. AW has also received grant support from Astellas Pharma. DF has received funding from the EU. DG has received consulting fees and lecture fees from Shire, Genzyme, Novartis AG, Sandoz, Pfizer, and Fresenius Medical Care Holdings. FWD has received funding from Amgen and Baxter. GL has received consulting fees from Amgen and Sandoz. GL has also received lecture fees from Amgen, Sandoz, Genzyme, and Shire. PJB has received consulting fees from Medtronic and has received grant support from Bardian and Novartis AG. RA has received consulting fees from Amgen, Abbott Laboratories, Merck, Affymax, Takeda Pharmaceutical Company, Daiichi Sankyo, Celgene, Watson Pharmaceuticals, and Rockwell Medical. RA has also received lecture fees from Abbott Laboratories, Merck, and Medscape. ZM has received lecture fees from Amgen, Shire, Genzyme, FMC, and Merck Sharp & Dohme. ZM has received grant support from Baxter, Amgen, FMC, Shire, and Genzyme. The remaining authors declared no competing interests.

REFERENCES
1. Aird WC. Phenotypic heterogeneity of the endothelium. I. Structure, function, and mechanisms. Circ Res 2007;100: 158–173.
2. Aird WC. Phenotypic heterogeneity of the endothelium. II. Representative vascular beds. Circ Res 2007;100: 173–190.
3. Tang EH, Vanhoutte PM. Endothelial dysfunction: a strategic target in the treatment of hypertension. *Pflugers Arch* 2010; **459**: 995–1004.

4. Deanfield J, Donald A, Ferri C et al. Endothelial function and dysfunction. Part I: Methodological issues for assessment in the different vascular beds: a statement by the Working Group on Endothelin and Endothelial Factors of the European Society of Hypertension. *J Hypertens* 2005; **23**: 7–17.

5. Brunner HR, Cockcroft JR, Deanfield J et al. Endothelial function and dysfunction. Part II: Association with cardiovascular risk factors and diseases: a statement by the Working Group on Endothelins and Endothelial Factors of the European Society of Hypertension. *J Hypertens* 2005; **23**: 233–246.

6. Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. *N Engl J Med* 2005; **352**: 1685–1695.

7. Kang DK, Kanellis J, Hugo C et al. Role of the microvascular endothelium in progressive renal disease. *J Am Soc Nephrol* 2002; **13**: 806–816.

8. Lerman A, Zeiher AM. Endothelial function: cardiac events. *Circulation* 2005; **111**: 363–368.

9. Danesh J, Wheeler JG, Hirschfield GM et al. C-reactive protein and other markers of inflammation in the prediction of coronary heart disease. *N Engl J Med* 2004; **350**: 1387–1397.

10. Ridker PM, Danielson E, Fonseca FA et al., Jupiter Study Group. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med* 2008; **359**: 2195–2207.