Frontiers in Nephrology: Viewing the Kidney through the Heart—Endothelial Dysfunction in Chronic Kidney Disease

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“Intestinal appendix! Kidney!” he said to himself, “It’s not a question of the appendix, not a question of the kidney, but a question of life and... death.”
—Leo Tolstoy, The Death of Ivan Ilyitch

Angina pectoris was first described by William Heberden in 1772, but the pathology of the disease awaited Edward Jenner’s description of an autopsy performed on one such patient. Jenner later wrote to a friend, “After having examined the more important parts of the heart, without finding anything by means of which I could account either for his sudden death or the symptoms preceding it, I was making a transverse section of the heart pretty near its base, when my knife struck against something so hard and gritty, as to notch it. I well remember looking up to ceiling, which was old and crumbling, conceiving that some plaster had fallen down. But on further scrutiny the real cause appeared: The coronaries were becoming bony canals.”

Inquisitive Jenner refused to publish these findings so as not to alarm his mentor and friend, John Hunter, who had experienced symptoms of angina pectoris.

As if repeating this history, the initial demonstration of accelerated atherosclerosis in patients with ESRD has not resonated among nephrologists for more than a decade. After this long delay, an avalanche of investigations has provided a somber picture of the prevalence and extent of atherosclerosis in patients with chronic kidney disease (CKD), which far exceeded that of the general population. These atherosclerotic manifestations, in today’s parlance, a large segment of a much broader syndrome of endothelial dysfunction, which afflicts the majority of patients with ESRD. A remarkable progress in our understanding of this syndrome has been achieved since the discovery of endothelium-derived relaxing factor and demonstration of its deficiency in patients with coronary artery disease even before the atherosclerotic plaques become detectable on angiograms.

This collection of Frontiers in Nephrology articles represents a selection of several most prominent, cutting-edge, at least in my opinion, yet least reviewed issues. Each of these subjects is introduced by its most prominent contributors. Not surprisingly, they all are cardiologists; what other subspecialty could have accumulated more knowledge of and insight into the problems of endothelial dysfunction? Undoubtedly, we would better serve our patients by establishing this dialog between cardiologists and nephrologists, because it may also be scientifically rewarding for practitioners of each discipline.

The presentations in this Frontiers in Nephrology flow from the general clinical presentations of atherosclerotic lesions (Gossl et al.) to the question of endogenous mechanisms of protecting endothelial lining, endothelial progenitor cells in particular, and the reasons that this mechanism fails in so many cases (Tongers and Losordo). This is followed by the exemplary pathway analysis of atherogenesis based on the investigations of the genomewide screening of affected arteries (Ashley et al.). This type of analysis, together with the concomitant study of the proteome of affected and nonaffected arteries, should be applied to examine some particular mechanisms involved in accelerated atherogenesis in patients with CKD; hence, the description would be instructive. Finally, an emerging class of nitric oxide donors conjugated to other formulations (e.g., with anti-inflammatory substances) that may afford potentially beneficial effects on endothelial dysfunction will be unveiled (Lettes and Loscalzo).

Application of these new ideas to the accelerated atherogenesis of CKD may require certain adjustments in view of the prominent role of “nontraditional” risk factors, such as asymmetric dim.
ethylarginine, homocysteine, and advanced glycation end products, to name a few. Intriguing is that these risk factors merge with the more traditional factors to impair basic functions of the endothelium: Vasorelaxation; anti-thrombotic and anti-inflammatory properties; maintenance of vascular permeability; and induction of oxidant stress, profibrotic phenotype, and endothelial lipodosis,14–22 as depicted in Figure 1. These actions clearly underscore the commonality of pathogenetic mechanisms leading to endothelial dysfunction.

There are several reasons to consider endothelial dysfunction as a heterogeneous syndrome. These reasons embrace not only the obvious diversity of causes and clinical presentations but also the discrepant outcomes of therapeutic interventions. This attempt to classify various forms and presentations of endothelial dysfunction, the syndrome that so far has been considered homogeneous and beyond the need for classification, is designed to distinguish between the following major heterologous groups and mechanisms: Spatial distinctions (local versus systemic), temporal distinctions (reversibility), clinical intensity, and dependence on specific risk factors or adverse effects of certain medications (Table 1). Individual patients presenting with signs of endothelial dysfunction may have diverse etiologic and/or mechanistic causes of the syndrome, which may present themselves in a variety of clinical manifestations. It would be our future goal to be able to gauge the severity of preclinical endothelial dysfunction using a combination of surrogate markers and devising an algorithm incorporating these markers and predicting the severity and site of clinical manifestations and optimal therapeutic interventions.

The history of investigations into atherogenesis provides ample examples of protracted time lapses, as it has occurred, for instance, with Anichkov’s discovery of the role of cholesterol in plaque formation, which remained dormant for four decades. It is hoped that such a sad ignorance will not repeat itself in our pursuits to define the causes and refine therapies of endothelial dysfunction and accelerated atherogenesis in patients with CKD.

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