Endothelial dysfunction in CKD: a new player in town?

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Endothelial dysfunction represents an obligatory, prodromal phase in the atherosclerosis process. Initially identified and thoroughly investigated in bench experiments, endothelial dysfunction has now progressed to a full-fledged outcome measure in clinical studies [1]. Endothelial function may be tested by two approaches [2]. The first is functional in nature and is based on the forearm haemodynamic response to acetylcholine (a pharmacological stimulus impinging upon the enzyme NO synthase) or to ischaemia [flow-mediated vasodilatation –(FMD) a physiological stimulus to the same enzyme]. The second approach rests on the measurement of the plasma concentration of specific biomarkers, i.e. a series of compounds, synthesized within the endothelium and that are released into the systemic circulation when endothelial integrity is hampered by noxious factors. The intercellular (ICAM) and vascular (VCAM) adhesion molecules, endothelial selectin (E-Selectin) and von Willebrand Factor (vWF) are currently held as the most reliable biomarkers of endothelial dysfunction/damage. The two approaches look at different aspects of endothelial function and therefore haemodynamic and biomarker-based tests provide complementary rather than overlapping information on endothelial integrity. Haemodynamic studies appear of particular value in clinical research, because altered endothelium-dependent vasoregulatory control predicts cardiovascular complications in a variety of clinical settings. Endothelial function testing is accepted as a valid surrogate endpoint in studies of cardiovascular prevention in children and adolescents. Chronic renal insufficiency is recognized as a clinical situation posing major risks to endothelial integrity [3]. However, there is still a paucity of haemodynamic studies of endothelial function in patients with chronic kidney disease (CKD).

Endothelial dysfunction in CKD

A coherent parallelism between the haemodynamic response to acetylcholine and the (estimated) GFR was reported in a large survey on subjects with untreated, uncomplicated arterial hypertension [4]. Beyond hypertension, this link was also reported in a population-based study where endothelial dysfunction (estimated by plasma vWF and VCAM-1) rose in parallel with renal function loss in elderly people [5]. In a sizeable group of patients with mild to severe renal insufficiency enrolled in a renal clinic in Birmingham (chronic renal impairment in Birmingham (CRIB) study), GFR was associated both with low-grade inflammation and with biomarkers of endothelial dysfunction even among patients with moderate renal impairment [6]. Haemodynamic endothelial dysfunction, as assessed by FMD and GFR, showed a coherent relationship in two studies in patients with moderate to severe renal insufficiency [7,8] and inflammation might have been a common trigger for both alterations [9]. With 400 CKD patients, the report of Mahmut Yilmaz et al. [10] in this issue of the journal totalled a study population larger by far than the aggregate number of patients enrolled in previous studies of this kind. Studies based on the haemodynamics of forearm blood flow are difficult to perform because of time constraints (these tests are time-consuming) and because of the difficulties encountered by clinical investigators in enrolling drug-free CKD patients. Policies of detection and treatment of CKD at Gulane Medical Centre in Turkey are hospital centered, which permitted investigators to recruit a considerable number of well-selected, drug-free patients thereby excluding several of the many potential confounding factors for the interpretation of the GFR–endothelial function link. These confounding factors include diabetes, smoking, marked proteinuria or concomitant drug treatment. Remarkably, the GFR–endothelial function link in Yilmaz’ series was much stronger than that in previous studies, perhaps reflecting the stringent selection process. The link between haemodynamically defined endothelial dysfunction and the GFR in this study population per se is a solid contribution in this area, decisively establishing renal function impairment as a most coherent clinical correlate of renal function loss.

The adipose tissue as a prime-time player in endothelial dysfunction

In recent years, a cross-talk between the adipose tissue and the endothelium has been discovered and the issue is being intensively investigated. The main pathophysiology...
pathways implicated in this link are illustrated in Figure 1. The most abundant adipose tissue cytokine and insulin-sensitizer, adiponectin, is solidly established as an endothelial protective factor, because it prevents TNF alpha-driven endothelial damage and facilitates endothelial repair [11]. This cytokine, which is deficient in obese and overweight persons, appears to be directly associated with the haemodynamic response to acetylcholine in the forearm [12], implying a protective role in vivo in man. On the other hand, leptin, an anorexigen peptide whose plasma concentration is directly associated with fat mass and insulin resistance, causes NO-dependent vasodilatation in aortic and mesenteric arteries [13], pointing to its direct, potentially protective effect on endothelial integrity. These links appear to be of particular relevance in patients with CKD, because both cytokines accumulate as renal function deteriorates.

**Adiponectin, Visfatin and endothelial function in CKD**

In the study by Yilmaz et al. [10], at crude (univariate) analysis, high adiponectin was paradoxically associated with severe compromised endothelial function. However, as expected after adjustment for C-reactive protein (CRP) and other risk factors, adiponectin was directly rather than inversely associated with endothelial function, an observation fully in keeping with the biological notion that this adipokine is an endothelium-protective factor. Although the authors did not comment on this finding, the change in the direction of the adiponectin–vascular function link brought about by multiple regression analysis further emphasizes the importance of appropriate statistical adjustments in studies testing the relationship of this protein with clinical endpoints [14]. Thus, data in CKD patients agree with the consolidated notion that low adiponectin is a marker of endothelial dysfunction. Since endothelial dysfunction is an obligatory early step in the atherosclerosis process, Yilmaz’ observations are in keeping with previous studies in ESRD, showing that adiponectin may serve to mitigate the high atherogenic risk of this condition [15]. Yet the independent, direct link between adiponectin and FMD, although statistically significant, appeared to be fairly small. This finding generates the hypothesis that the favourable risk profile associated with high adiponectin, in some studies in ESRD and in high risk populations, may at least in part be independent of the anti-atherogenic effects of this compound—a possibility in keeping with the multifaceted biological role of adiponectin which extends to cell proliferation and angiogenesis [16].

Visfatin is the most recently identified adipose tissue cytokine. This compound is mainly synthesized in visceral fat and is associated with visceral but not subcutaneous fat composition [17]. A role of this novel adipokine in obesity is suggested by the observation that its plasma levels parallel the development of spontaneous obesity in KKAy mice [17]. In a recent study in patients with type 2 diabetes [18], Visfatin was strongly and inversely associated with FMD. Yilmaz et al. now show that this association holds true in non-diabetic CKD patients. It is remarkable that at multivariate analysis, the Visfatin–endothelial function link in these patients was stronger than that of other established risk factors for endothelial dysfunction like age, HOMA index, CRP and hypertension. Thus, data in type 2 diabetics and in CKD patients suggest that high Visfatin

**Fig. 1.** The relationship between adipose tissue cytokines and the endothelium. The aggregate of available studies on these cytokines is classified as definitively (+++), most likely (++) or probably (+) proving the hypothesized effect of the corresponding cytokine. IL-6 and TNF-α cause endothelial dysfunction and damage indirectly, i.e. by stimulating the synthesis of C-reactive protein (CRP) in the liver. CRP is a well-recognized risk factor for endothelial dysfunction.
may be implicated in endothelial dysfunction under these conditions.

Visfatin has been directly associated with beta-cell function deterioration [19] but in type 2 diabetics the plasma concentration of this substance is unrelated to insulin sensitivity as well as to adiponectin, CRP and fibrinogen [18]. In contrast, in non-diabetic CKD patients studied by Yilmaz et al. [10], both adiponectin and Visfatin correlated directly and quite strongly with CRP levels and with GFR. Thus the association pattern of biomarkers of inflammation and endothelial dysfunction in CKD patients differs from that of type 2 diabetes and therefore the two conditions cannot be considered equivalent models for studying the interference of Visfatin with endothelial function. Visfatin may play a role in the amelioration of insulin sensitivity induced by PPAR-γ agonists in type 2 diabetics [18], which contrasts with its negative effect on vascular function suggested by the Takebayashi et al. [18] and Yilmaz et al. [10] studies. Thus, at variance with adiponectin, which also exerts beneficial effects on both glucose metabolism and endothelial function, Visfatin may be a Janus compound, with contrasting metabolic and vascular effects. At this stage of knowledge it is worth emphasizing that the hypothesis, that Visfatin has a role in vascular function regulation, rests only on cross-sectional data in two complex diseases (type 2 diabetes and CKD), i.e. two conditions where a variety of factors concur to disturb endothelial function. In this type of study, confounding by unknown or unaccounted risk factors and/or residual confounding by accounted risk factors cannot a priori be excluded, which still leaves the question open as to whether or not Visfatin truly perturbs endothelial function. At variance with adiponectin, where clinical observations followed solid biological knowledge highlighting a role of this adipokine in vascular protection, to date there is no experimental study exploring the effect of Visfatin on endothelial cells or in suitable experimental models allowing direct testing of its interference with endothelial function. Thus, the intriguing data by Yilmaz et al. should be considered as hypothesis generating rather than as hypothesis testing. Investigators in the field should now move from the clinic to the bench to see whether Visfatin perturbs vascular function. The possibility that Visfatin adds to the list of factors influencing vascular function and repair is suggested by the recent observation that it impinges upon the regulation of angiogenesis [20]. Furthermore, cohort studies are needed to see whether high Visfatin heralds cardiovascular outcomes in patients with mild renal insufficiency: the Hoorn study. J Am Soc Nephrol 2006; 17: S64–S68


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References


