Endothelial dysfunction, atherosclerosis and thrombosis in uremia – possibilities of intervention

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Abstract

Chronic renal failure is a state of prominent endothelial dysfunction, accelerated atherosclerosis, high incidence of thromboembolic complications and excess cardiovascular mortality. We reviewed up-to-date experimental and clinical data showing close and deleterious links between these entities. Emerging therapeutic interventions aimed at improvement of endothelial function and better clinical outcomes in chronic kidney disease patients were also discussed.

Key words: atherosclerosis, cardiovascular disease, endothelium, thrombosis, uremia.

Introduction

Although uremia is regarded as a clinical model of bleeding diathesis, nowadays a tendency to thrombosis prevails in these patients. Atherosclerosis and thrombotic complications are the main causes of morbidity and mortality in different stages of chronic kidney disease, particularly in patients with renal failure.

In vivo the most important interaction in hemostasis is the one between platelets and vascular endothelium. Platelet function is usually impaired in uremia, although enhanced platelet aggregation in dialyzed patients has been demonstrated [1].

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Received 6.05.2004 Accepted 7.06.2004

Antithrombotic function of endothelium

Endothelium produces many substances (*Tab. 1*) with autocrine and paracrine activity [2]. Factors which are regulated by the endothelium and take active part in hemostasis and thrombosis are shown in *Tab. 2*.

One of the most important functions of endothelial cells is the prevention of non-physiological activation of blood coagulation resulting in thrombosis. This activity is mediated by the negative charge of the endothelium provided by surface expression of heparan sulfate proteoglycans and the secretion of prostacyclin, nitric oxide (NO), tissue factor pathway inhibitor (TFPI) and tissue plasminogen activator (t-PA). Endothelial expression of thrombomodulin (TM), which binds to thrombin and activates anticoagulant protein C, plays a very important antithrombotic role. A concentration-dependent role of TM in modulating activity of thrombin activatable fibrinolysis inhibitor (TAFI) is also acknowledged. Endothelial damage triggers thrombus formation due to decreased antithrombotic potential, expression of tissue factor (TF) and release of von Willebrand factor (vWf) as well as plasminogen activator inhibitor (PAI-1). Vascular tone, leukocyte adhesion, permeability to nutrients, macromolecules and leukocytes is also normally regulated by the endothelium. It has become increasingly evident that the peripheral vasculature exhibits striking regional and segmental heterogeneity in the influence of the endothelial cell layer on vascular tone. This heterogeneity arises in part from differences in the endothelial cell microenvironment (autocrine and paracrine substances), and in the influence of hemodynamic forces, such as local pressure and shear stress. Endothelial cells produce also vasoconstrictive substances like endothelin-1 and thromboxane A_2. A delicate balance between endothelium-derived relaxing and contracting factors maintains vascular homeostasis. Upon disruption of this balance by inflammatory and traditional cardiovascular offenders, the vasculature becomes susceptible to atheroma formation. Inflammatory mediators appear to play a fundamental role in the initiation, progression and the eventual rupture of the atherosclerotic plaque.

Table 1. **Autocrine and paracrine substances released from the endothelium (according to Verma et al.)**

Vasodilators	NO, prostacyclin, endothelium-derived hyperpolarizing factor, bradykinin, adrenomedullin, C-natriuretic peptide
Vasoconstrictors	ET-1, angiotensin-II, thromboxane A_2, oxidant radicals, prostaglandin H_2
Antiproliferative	NO, prostacyclin, transforming growth factor-β, heparan sulphate
Proproliferative	ET-1, angiotensin-II, oxidant radicals, platelet-derived growth factor, basic fibroblast growth factor, insulin-like growth factor, interleukins
Antithrombotic	NO, prostacyclin, plasminogen activator, protein C, tissue factor inhibitor
Prothrombotic	ET-1, oxidant radicals, plasminogen-activator inhibitor-1, von Willebrand factor, thromboxane A_2, fibrinogen, tissue factor
Inflammatory markers	CAMs (P- and E-selectin, ICAM, VCAM), chemokines, nuclear factor κ-B
Permeability	Receptor for advanced glycosylation end-products
Angiogenesis	Vascular endothelial growth factor

Table 2. **Regulation of hemostasis and thrombosis by the endothelium (according to Cines et al.)**

	Antithrombotic	**Prothrombotic**
Coagulation protein binding sites	Glycosaminoglycans/ATIII TFPI Thrombomodulin	Binding sites for: fibrin, FIX, IXa, X, Xa, FXII, kallikrein Tissue factor Thrombin receptor Receptor for protein C/APC
Substances produced and/or stored by platelets	PGI_2 NO ADPase	vWF PAF Fibrinogen FV FXI
Fibrinolytic factors	t-PA production u-PA expression u-PAR Plasminogen binding sites Annexin II	PAI-1, PAI-2 PAI-3 (protein C inhibitor) TAFI activation
Vasomotor factors	NO PGI_2	TxA_2 ET-1

Nitric oxide is a particularly important endothelium-derived mediator because of its unique vasodilatory, antiplatelet, antiproliferative, antiadhesive, permeability-decreasing and antiinflammatory properties.

Dysfunction of the endothelium, inflammation and thrombosis

Endothelial dysfunction prevails when endothelial properties have changed in a way that is inappropriate with regard to the preservation of organ function [3]. For example increased vascular tone and permeability may contribute to increased blood pressure and atherogenesis. Current concepts recognize atherosclerosis as a dynamic and progressive disease arising from the combination of endothelial dysfunction and inflammation [4]. Endothelial dysfunction leads to the loss of its antithrombotic and profibrinolytic properties and the development of a prothrombotic and antifibrinolytic status. Such alterations may differ depending on the extent of the injury and intrinsic properties of the endothelium (i.e. venous vs arterial vs microvascular). Endothelial activation designates one specific type of endothelial dysfunction characterized by increased cytokine-induced interactions with blood leukocytes, where adhesion molecules and chemoattractants become essential [3]. Endothelial cell dysfunction can promote transduction of atherogenic risk factors, thus playing an important role in the initiation and progression of atherosclerosis. Oxidatively modified low-density lipoproteins (oxLDL), cholesterol, smoking, hypertension, angiotensin II and diabetes may initiate atherosclerosis through endothelial activation. The predilection of atherosclerosis to arterial branching points is explained by nonlaminar or even turbulent blood flow, which increases shear stress and activates endothelial cells. Endothelial function cannot be measured directly in humans, thus indirect estimates are often used in clinical research, including endothelium-

dependent vasodilation and plasma levels of endothelium-derived substances such as NO, vWf, soluble TM, endothelin, circulating adhesion molecules, t-PA and PAI-1.

Lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1) is a novel mediator of endothelial cell activation [5]. In addition to being the main receptor for oxLDL, LOX-1 has the ability to bind damaged or apoptotic cells and activated platelets, and reduce the intracellular concentration of NO in endothelial cells [6]. Protease-activated receptors (PARs) are G-protein-coupled receptors which link tissue injury with appropriate cellular responses, such as inflammation and tissue repair, both of which may contribute to disease progression [7]. There are four PARs out of which three (PAR-1, PAR-3, and PAR-4) are activated by thrombin. PARs are expressed by a variety of cells including endothelial cells and platelets. Their signaling impacts the initiation, progression, and complications of atherosclerosis.

Injured vascular endothelium may be repaired thanks to bone marrow-derived endothelial progenitor cells which have an ability to differentiate into functional endothelial cells [8].

Endothelial dysfunction and thrombosis in uremic patients

Growing amount of evidence indicates that endothelial function is disturbed in uremic patients. In line is the fact that forearm artery dilatation is strictly related to the degree of glomerular filtration rate (GFR) [9]. High levels of endothelium-derived regulatory proteins including antifibrinolytic and prothrombotic PAI-1 have also been observed. As PAI-1 is produced not only by endothelial cells but also by hepatocytes, adipocytes and vascular smooth muscle cells, a panel of endothelium derived substances should be determined to validate the assumption of endothelial dysfunction or damage. Several of these molecules are increased in concert in uremia [10]. There is a strong correlation between plasma levels of PAI-1 and the prevalence of cardiovascular disease in uremia [11]. Elevated TF levels as well as increased concentrations of vWf were also described in uremic patients [12-14].

Endothelial dysfunction is also likely to be due to oxidative stress which increases in different stages of chronic kidney disease, including uremia [15-17]. Markers of oxidative stress, endothelial injury, extrinsic coagulation pathway activation and intima-media thickness of the carotid artery were strictly related with the presence of coronary heart disease in hemodialysis (HD) patients [16]. Moreover, oxLDL are cytotoxic for endothelial cells. In hypertensive patients with reduced creatinine clearance plasma fibrinogen, prothrombin fragment 1 + 2 (a marker of thrombin activation) and D dimer (a marker of thrombosis) were elevated. In uremic patients increased blood concentrations of fibrinogen, fibrinopeptide A and thrombin-antithrombin complexes (markers of thrombin activity) were observed [18]. Decreased activity of protein C was demonstrated in patients with renal failure [19]; there is also a report on low levels of free protein S and an active anticoagulant fraction of protein C in these patients [20].

Endothelial dysfunction may play a role in the progression of chronic renal failure by increasing intraglomerular pressure and glomerular basement membrane permeability, as well as indirectly – by influencing mesangial cell and podocyte function in a paracrine fashion. Inflammatory cytokines are also likely to be involved, as uremia can be considered a state of chronic low-grade inflammation.

Thrombosis and atherosclerosis in uremic patients

In uremic patients a striking association of inflammation, high fibrinogen levels and thrombosis was observed [21]. Hypoalbuminemia – a result of malnutrition and/or inflammation, is strongly associated with arteriovenous (AV) graft thrombosis in HD patients [22]. Endothelial cell activation, vascular smooth muscle proliferation and extracellular matrix deposition are also known risk factors for AV graft thrombosis [23]. Assessment of circulating PAI-1 levels can identify patients who are at risk for developing atheromatous cardiovascular disease [11].

Coronary artery thrombosis is generally a result of atherosclerosis, which develops primarily as a result of endothelial damage. Atherosclerosis is a very frequent complication in uremia due to coexistence of hypertension, hyperhomocysteinemia, inflammation, malnutrition and increased oxidative stress. Elevated triglycerides, intermediate-density and very-low-density lipoproteins as well as lipoprotein A, and lowered high-density lipoproteins increase the risk of atherosclerosis in end-stage renal disease [24].

Thrombotic events may also be associated with renal transplantation. Antibody-mediated or cyclosporine-induced endothelial damage may play an important prothrombotic role.

The most common type of thrombosis in uremia results from disruption of the vulnerable atherosclerotic plaque. This is a consequence of exposure to hemodynamic stress. Erosion of the plaque, characterized by areas of endothelial cell desquamation, exposes a prothrombotic surface. Even greater prothrombotic stimulus arises from the rupture of fibrous cap and removal of its contents into the lumen. Subendothelial collagen, TF and vWf become accessible in circulation, promoting coagulation and thrombin formation [4]. Then, platelet activation and aggregation ensue, mediated by interaction with thrombin, TF and vWf. Tissue factor overexpression by endothelial cells and macrophages is enhanced by the presence of inflammatory mediators within the plaque, namely interleukin-1, tumor necrosis factor (TNF) alpha, and CD40/CD40L – members of the TNF family. In response to this vascular insult, thrombogenicity is further favored by the activation of PARs on platelets and in the adjacent tissue [7].

Treatment

Specific interventions which could heal the diseased endothelium in renal failure patients are not available. Smoking cessation, use of ultrapure dialysis fluid and biocompatible membranes for HD procedures, administration of statins,

angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, endothelin blockers, estrogens, L-arginine, antioxidants and folic acid are, however, likely to improve some aspects of endothelial function.

Angiotensin-converting enzyme inhibitors decrease the levels of PAI-1 in plasma, thus promoting fibrinolysis. They also have antioxidative properties and cause a decrease in angiotensin-II and an increase in bradykinin activity. Angiotensin receptor blockers seem to act in a similar way although they do not increase the bradykinin activity.

Reduction of oxidative stress during HD may be reached by the use of biocompatible membranes and ultrapure dialysis fluid. Hypercholesterolemia, hyperhomocysteinemia and smoking are associated with a marked increase of asymmetric dimethylarginine (ADMA) – a known NO synthase inhibitor. Antioxidants, like vitamin C and vitamin E, have been used in uremic patients quite extensively. The lowering of reactive oxygen species in patients treated with vitamin C positively influenced their survival [25]. Nitric oxide is generated in the endothelium from L-arginine by NO synthase. In uremia L-arginine availability may be low [26]. Tetrahydrobiopterin is an essential factor for NO synthase function. When tetrahydrobiopterin is oxidized, the synthesis of NO is compromised and superoxide-peroxynitrite is generated from NO, thus amplifying the oxidative stress [27]. Vitamin C and selenium-containing glutathione peroxidase may reconvert tetrahydrobiopterin to the non-oxidized state, which normalizes NO production. A negative effect of vitamin C on an increase of serum uric acid level in uremia should be taken into account. Selenium supplementation has not been properly controlled. Quite safe may be vitamin E, which can be used orally or as vitamin E-modified cellulose membranes for HD; the clinical results are, however, conflicting and the dialysis cost is substantially increased [28,29]. The placebo-controlled SPACE study showed reduction in myocardial infarction and composite outcome of cardiovascular end-points in HD patients treated with 800 IU of vitamin E daily [30]. Red blood cells contain a high amount of antioxidants – particularly of reduced glutathione peroxidase, so anemia treatment should be included into antioxidative armamentarium. It is also interesting that combination of antioxidants with simvastatin and niacin blunted the favorable effects of lipid-lowering drugs [31]. Acetylcysteine may also be useful as an antioxidant in renal failure patients [32].

There are conflicting data concerning the use of estrogens which are beneficial to endothelium in experimental studies but did not meet expectancies in clinical trials. Supplementation of estrogens to post-menopausal women resulted in even higher coronary events rate. There are inconclusive data concerning the use of folic acid to diminish plasma concentration of homocysteine in uremic patients. In contrast to studies describing hyperhomocysteinemia as a risk factor for cardiovascular events, a recent study found a reverse relationship between homocysteine concentration and both mortality and cardiovascular events in uremic patients [33]. Administration of high-dose folic acid did not affect either mortality or cardiovascular morbidity in that population. In another prospective study a low, rather than a high, plasma homocysteine was an indicator of poor outcome in HD patients [34]. The result may be explained by nutritional feature of homocysteine which is low in malnourished patients.

Statins, among other pleiotropic actions may exert a beneficial effect on the endothelium and increase fibrinolysis. A lag time in a clearly superior effect of statin as compared to placebo in 4S Study [35] and Heart Protection Study [36] suggests an indirect effect of statins, possibly via a beneficial effect on the endothelium. However no lag time was found in recent controlled trials labeled with acronyms REVERSAL [37] and PROVE-IT [38], comparing head-to-head atorvastatin and pravastatin effect on reversing atherosclerotic coronary disease. Both the statins lowered serum C-reactive protein levels – in PROVE-IT Study by over 80%. This suggests a very potent antiinflammatory effect, particularly evident for atorvastatin. Apart from many trials statins have been under-used in uremics, probably due to the high cost of such therapy. As atorvastatin does not need dose adjustment in renal failure (similarly to fluvastatin and pravastatin) it seems to be a drug of choice in patients with chronic kidney disease. It cannot be, however, excluded that new statins like rosuvastatin will be superior to atorvastatin in these patients.

Possible pharmacological prophylaxis of AV graft thrombosis includes antiplatelet agents, anticoagulants, and antiproliferative agents administered either systemically or locally [39]. Recent multicenter placebo-controlled trial of aspirin plus clopidogrel for prevention of AV graft thrombosis was discontinued due to increased risk of bleeding [40].

Clear benefits were established in treatment of acute coronary syndromes with aspirin and heparin, despite the risk of bleeding in chronic renal failure. Also thrombolytic agents or glycoprotein IIb/IIIa inhibitors may be additionally administered if otherwise indicated [41]. Dose adjustments for GFR is necessary for some glycoprotein IIb/IIIa inhibitors. Abciximab appears to be the drug of choice in uremic patients as its dose does not need to be adjusted.

Thrombosis is a serious complication of renal transplantation. No association of renal vein thrombosis with cyclosporine or azathioprine use was demonstrated in a randomized trial [42]. However, cyclosporine A may induce endothelial damage and increase a tendency to thrombosis. In case of hemolytic uremic syndrome/thrombotic thrombocytopenic purpura in a patient treated with calcineurine inhibitor, the drug should be switched or totally withdrawn.

Antithrombotic agents such as heparin and oral anticoagulants are commonly used in uremic patients, although both the treatments need scrupulous monitoring, the same concerns antiplatelet aspirin. Heparin has been extensively used as an anticoagulant during HD procedures. It exerts pleiotropic effects which may be of clinical value. Heparin can release from the endothelium several substances including growth factors (i.e. activin A and follistatin) to the circulation. Recently it was shown that activin A is a potent activator of renal interstitial fibroblasts [43]. The role of follistatin – a natural inhibitor of activin A, may be thus of antifibrotic value. Hepatocyte growth factor, which is also released from the endothelium by heparin, ameliorates renal fibrosis by enhancing extracellular matrix catabolism via both the metalloproteinase and plasminogen activators/plasmin proteolytic pathways [44]. Oral anticoagu-

lants are usually used in uremic patients with persistent atrial fibrillation as a protection from the thromboemboli formation or as prophylaxis of recurrence of deep venous thrombosis. They did not, however, prove to be useful in protection against native AV fistula or synthetic graft thrombosis.

In conclusion, endothelial dysfunction is a prominent feature in patients with renal failure, underlying accelerated atherosclerosis and a high incidence of thromboembolic cardiovascular complications. Specific therapeutic interventions aimed at the endothelium hold exceptional promise for better survival in this population.

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