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Is there a link between CD146, a novel adhesion molecule and other markers of endothelial dysfunction in nephrotic syndrome and continuous ambulatory peritoneal dialysis?

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Abstract

Background: CD146 is a novel cell adhesion molecule localized at the endothelial junction. Its increased plasma levels in chronic renal failure are linked to endothelial dysfunction. Endothelial dysfunction and hemostatic disturbances, a common feature of nephrotic syndrome (NS), mimics a state of protein loosing by peritoneal membrane in patients on chronic ambulatory peritoneal dialyses (CAPD). The aim of the study was to assess CD146 in relation to other markers of endothelial cell injury in patients with NS in comparison to patients on CAPD.
Materials and methods: We studied 45 CAPD patients, 43 patients with nephrotic syndrome and 25 healthy volunteers. Markers of endothelial cell injury: TFPI total, full length, truncated, von Willebrand factor, trombomodulin, P-selectin, E-selectin, ICAM, VCAM and CD146 were assessed using commercially available kits.
Results: All these markers studied except selectins were significantly elevated in patients with NS and CAPD when compared to the healthy volunteers. In CAPD, VCAM, thrombomodulin and CD146 were significantly elevated over NS patients. CD146 correlated significantly with ICAM as well as total and truncated TFPI in CAPD patients. Moreover, total TFPI was positively related to VCAM. CD146 correlated with ICAM in NS, whereas in healthy volunteers CD146 correlated only with TFPI concentration.
Conclusions: Our studies indicate that in nephrotic patients, as well as in CAPD, there is an evidence of endothelial cell injury. Correlations between CD146 and

Abbreviations: CAPD, continuous, ambulatory peritoneal dialysis; ICAM, intercellular cell adhesion molecule; NS, nephrotic syndrome; TFPI, tissue factor pathway inhibitor; VCAM, vascular cell adhesion molecule.

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adhesion molecules and TFPI might further support its use as a endothelial cell function marker.

Introduction

Changes in endothelial cell function, which may be interpreted as a response to injurious stimuli, are an important component of the pathogenesis of atherosclerosis and thrombosis [1]. This is not surprising since vascular endothelium synthesized many substances involved in the regulation of coagulation and fibrinolysis, vessel tone and permeability. However, the assessment of endothelial cell injury in vivo is complex due to multifunctional nature of these cells. Exposure of endothelial cells to oxidized LDL in vitro releases various adhesion molecules including vascular cell adhesion molecule (VCAM), intercellular cell adhesion molecule (ICAM), selectins and von Willebrand factor-vWF [2], which are considered as markers of endothelial cell injury. On the other hand, vascular endothelium provides effective anticoagulant properties by expressing surface bound proteoglycans, such as heparan sulfate and thrombomodulin, and by releasing coagulation factors inhibitors, such as protein S and tissue factor pathway inhibitor (TFPI) [3]. However, it is still unclear which endothelial marker is more sensitive in predicting simple or more serious cardiovascular complications. Signs of endothelial dysfunction have been reported in chronic renal failure and in dialyzed patients [4–7]. Moreover, cardiovascular complications are the most common cause of death in dialyzed patients together with increased incidence in coronary heart disease [8] in nephrotic syndrome (NS).

CD146 is a novel cell adhesion molecule localized at the endothelial junction and constitutively expressed in all human endothelium irrespective of anatomical site or vessel calibers [9]. A rise in CD146 expression, detectable on HUVEC treated with inflammatory cytokines [9], suggests that endothelial activation modulates its expression. Bardin et al. [10] suggested that increased plasma CD146 levels in chronic renal failure, was linked to endothelial junctional alteration.

Ours [4] and other previous studies [11] indicated that chronic ambulatory peritoneal dialysis (CAPD) patients present a hypercoagulable state and endothelium dysfunction as well as patients with nephrotic syndrome [12]. Up to authors' knowledge, there are no data about CD146 levels in patients on CAPD or with nephrotic syndrome. In the recent paper of Bardin et al. [10], correlations between CD146 and other markers of endothelial cell injury were not studied in patients with chronic renal failure.

In the light of these observations, we decided to explore the link between CD146 and concentrations of some markers of endothelial activation/dysfunction in patients with nephrotic syndrome and on CAPD. In this study, we therefore evaluated the relationships between CD146 and thrombomodulin, von Willebrand factor, considered a markers of endothelial damage, as well as relationships between CD146 and adhesion molecules and TFPI, considered also as markers of endothelial dysfunction [13].

Materials and methods

The study was performed on 43 patients with nephrotic syndrome (age range 21–72 years, 24F, 19M, mean BMI 23.85±3.7 kg/m^2) and 45 patients maintained on CAPD (age range 22–71 years, 26F, 21M, mean BMI 24.0±4.0 kg/m^2). Inclusion criteria were: a stable clinical state, no thrombosis or inflammation (C-reactive protein within normal range), absence of cardiovascular complications (including uncontrolled hypertension), no diabetes, no oral contraception in women of child-bearing age, stable and no more than twice of the normal asparaginase and alanine animotransferases (AspAT and AlAT) activities. None of the patients investigated had received blood transfusions for at least 1.5 months and no drugs known to affect hemostasis were administered for at least 2 weeks prior the study. All the subjects were biopsied and histopathological diagnosis was established as follows: IgA nephropathy in 9 cases, membranoproliferative glomerulonephritis in 6 cases, membranous nephropathy in 6 cases, focal segmental glomerulosclerosis in 15 cases and minimal change glomerulonephritis in 2 cases. Biopsy was not diagnostic in four cases. During the study, none of the patients have received prednisone, anticoagulants or cytotoxic drugs. In CAPD patients, renal failure was due to glomerulonephritis (n=21), chronic interstitial nephritis (n=9), polycystic kidney disease (n=6) and other lub unknown causes (n=9). All the patients were informed about the aim of the study and gave their consent. The study was approved by local Ethics Committee.