

Endocan: A New Molecule Playing a Role in the Development of Hypertension and Chronic Kidney Disease?

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Recently, endocan—formerly known as endothelial cell-specific molecule 1 (ESM-1)—was found to be associated with entities such as cancer, hypertension, renal transplant rejection, and chronic renal failure. Endothelial cells of many organs secrete endocan, but the exact functions of this relatively new molecule have not been elucidated completely. Emerging evidence suggests, however, that endocan plays an important role in inflammation,

upregulation of cell adhesion molecules, lymphocyte functions, and endothelial cytoskeleton rearrangement. As suggested above, endocan has a prognostic impact in hypertension, transplant rejection, and chronic renal failure. In the current review, the evidence regarding endocan, hypertension, and chronic renal failure are summarized. *J Clin Hypertens (Greenwich)*. 2014;1–3. © 2014 Wiley Periodicals, Inc.

In the past few years, the vascular endothelium has been shown to play a crucial role in inflammation, coagulation, angiogenesis, and tumor invasion, primarily through regulation of receptor/ligand interactions and secretion of different mediators. One of the molecules secreted by endothelial cells is endothelial cell-specific molecule 1 (ESM-1).¹ The carbohydrate moiety of ESM-1 is a single chain of the dermatan sulfate proteoglycan comprising a mature polypeptide of 165 amino acids. Because this proteoglycan is specifically secreted by endothelial cells, the name proposed was “endocan.”²

Endocan is secreted by vascular endothelial cells in the skin, kidney, gastrointestinal tract, lungs, liver, brain, lymph nodes, heart, and thyroid gland.³ Normally, endocan is proposed to have a major role in the regulation of cell adhesion, inflammatory disorders, and tumor progression. Endocan has been shown to have prognostic value in various pathologic entities, such as cancer, sepsis, inflammatory disorders, hypertension (HTN), transplant rejection, and chronic kidney disease.^{4–13}

In the current review, we summarize the recent findings regarding endocan and disease states, specifically focusing on HTN, chronic kidney disease, renal transplantation, underlying potential mechanisms, and future perspectives.

ENDOCAN AND HTN

Since endothelial dysfunction, atherosclerosis, and HTN are related with each other and since endocan is linked

with endothelial dysfunction and inflammation, it was suggested that endocan might also be related to HTN.¹¹

Indeed, in one pilot study, the relationship between endocan and HTN was investigated. Balta and colleagues showed that endocan levels were higher in newly diagnosed hypertensive patients compared with normotensive patients. Furthermore, endocan levels correlated with carotid intima-media thickness and high-sensitivity C-reactive protein (hsCRP).¹¹ However, this study had many drawbacks including low patient numbers, not using ambulatory blood pressure, and lack of data regarding echocardiographic parameters.

In another study, the effect of calcium channel blocker (amlodipine) treatment on serum endocan levels and endothelial cell adhesion molecules were investigated in patients with essential HTN. Patients were treated with amlodipine 5 mg/d to 10 mg/d for 8 weeks and blood samples were taken at the beginning and after an 8-week period. Following treatment, intracellular cell adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1) levels decreased while E-selectin increased. Endocan levels tended to decrease ($P=.063$). On the other hand, the CD11a/lymphocyte function-associated antigen 1 (LFA-1) ICAM-1 and endocan ligand was significantly increased in lymphocytes, monocytes, and granulocytes. Thus, the authors concluded that the increased expression of ICAM/VCAM ligands, together with a decrease of soluble cell adhesion molecules and endocan, suggest a de-activation of endothelium consecutive to a reduction in blood pressure by amlodipine in hypertensive patients.¹⁴

ENDOCAN AND RENAL TRANSPLANTATION

First reports came from Li and colleagues investigating the prognostic utility of ESM-1—a precursor of endocan—in acute rejection after renal transplantation. This study has demonstrated that in patients with acute rejection, ESM-1 mRNA and protein expression

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increased significantly. The authors concluded that ESM-1 appeared to reflect the degree of endothelial cell injury in renal allografts and might have the potential to serve as a highly sensitive and specific marker for acute rejection after renal transplantation.¹⁵

Soon after this initial report, another study examined the relationship between endocan levels and chronic renal allograft injury in renal transplant patients. Su and colleagues recruited 97 renal transplant patients with a mean age of 43.6 ± 13.2 years and with a mean transplant duration of 7.0 ± 5.7 years. They demonstrated that higher endocan levels were found in more advanced chronic kidney disease (CKD) stages in a dose-dependent manner and that endocan levels were inversely correlated with estimated glomerular filtration rate. In addition, renal function decline was significantly greater in the group with higher serum endocan levels. Moreover, tumor necrosis factor α (TNF- α) correlated with endocan and TNF- α -activated human umbilical vein endothelial cells secrete high levels of endocan and transforming growth factor β 1. All these findings suggest a relationship between endocan and endothelial dysfunction.¹²

ENDOCAN AND CKD

Very recently, we investigated the relationship between plasma endocan levels and inflammation, endothelial dysfunction, cardiovascular events, and survival in CKD. A total of 251 patients with CKD (stage 1–5) not undergoing dialysis were recruited. Plasma endocan concentrations were negatively correlated with estimated glomerular filtration rate and positively correlated with inflammatory markers such as pentraxin 3 (PTX3) and hsCRP. In addition, endocan was associated with endothelial dysfunction as evaluated by flow-mediated vasodilatation (FMD) and carotid intima-media thickness (CIMT). More importantly, after adjusting for multiple confounders, endocan levels were independently associated with cardiovascular events (hazard ratio, 3.54; 95% confidence interval [CI], 2.36–5.28) and all-cause mortality (hazard ratio, 2.38; 95% CI, 1.17–4.82). In addition, the authors demonstrated some important and interesting findings. Using receiver operating curve analysis, endocan had an area under the receiver operating curve for survival of 0.774 (95% CI, 0.717–0.824; $P < .001$), which was greater than that of estimated glomerular filtration rate, proteinuria, FMD, CIMT, hsCRP, and PTX3. The discriminative power for predicting cardiovascular events was also significantly higher for endocan (area under the corresponding receiver operating characteristic curve, 0.851; 95% CI, 0.800–0.892; $P < .001$) than for all of the already mentioned variables.¹³

POSSIBLE MECHANISMS OF ACTION

Why does endocan appear to be related to worse outcomes and what are its deleterious actions *in vivo*? These are relevant questions but unfortunately the answers are not completely known, although some insights emerged from previous studies. These include:

- Upregulation of cell adhesion molecules, such as ICAM-1, LFA-1, VCAM-1, and E-selectin, helping leukocyte extravasation.^{12,16–18}
- Inhibition of the interaction between ICAM-1 and LFA-1 on leukocytes.
- Endothelial cell activation by induction of molecules such as resistin.¹⁹
- Close relationship with systemic inflammatory markers such as CRP and PTX3.¹³
- Endothelial cytoskeleton rearrangement and increased cytoskeleton-associated protein secretion such as zonula occludens leading to cellular contraction.¹⁷

HOW DOES ENDOCAN AFFECT PROGNOSIS IN CKD AND HTN?

All above-mentioned mechanisms regarding endocan may play a role in different stages; however, growing experimental evidence suggests that inflammation plays a major role in HTN. Along these lines, it was demonstrated that lymphocyte infiltration occurs in experimental models of HTN.²⁰ At the same time, perivascular lymphocyte infiltration impairs vasodilatation and increases contractility.²¹ Besides, in angiotensin II-dependent HTN, lymphocyte deficiency facilitates natriuresis likely via stimulation of endothelial nitric oxide synthase- and cyclooxygenase-2-dependent pathways.²²

Thus, endocan may affect these pathways and lead to HTN and chronic kidney disease. The hypothetical effects of endocan on the development of HTN, CKD, and cardiovascular disease are shown in the Figure.

FUTURE PERSPECTIVES

The specific relationship between endocan and end organ damage such as cardiac hypertrophy, renal damage, and stroke must be determined. In addition, the role of endocan in different diseases such as in dialysis patients and in patients with diabetes must be studied. The specific relationship between endocan and

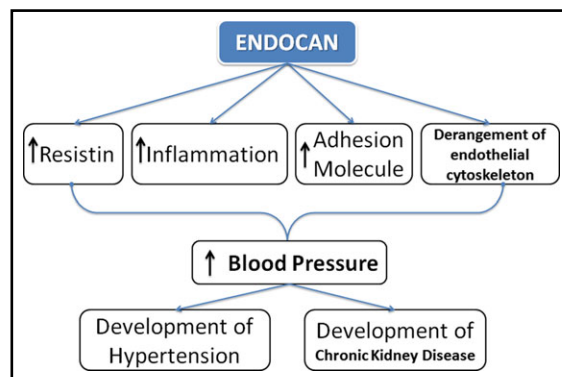


FIGURE. The hypothetical effects of endocan on the development of hypertension, chronic kidney disease, and cardiovascular disease.

heart disease should be more intensively studied. For example, a recent study showed that endocan may be related to severity of coronary artery disease.²³ Kinetics of endocan should be studied in different disease stages such as sepsis and diabetes, as opposed to single-measurement studies. The role of endocan in the renin angiotensin system, sympathetic system, and oxidative stress and the treatment with anti-endocan antibodies to possibly improve HTN, endothelial dysfunction, and transplant rejection must be determined. For example, experimental evidence suggests that treatment with anti-endocan antibody improved survival in patients with sepsis.¹⁸

CONCLUSIONS

Endocan—an emerging molecule secreted by endothelial cells—seems to have many roles in pathologic processes. It has a prognostic implication in various pathologic conditions such as cancer, sepsis, CKD, renal transplant rejection, and HTN. Various pathophysiologic processes that result in endothelial dysfunction attributable to endocan likely play a role in these outcomes. Further studies are needed to highlight whether endocan is only a marker of a negative prognosis in these conditions or whether it has an active role.

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