Hypertension Research (2024) 47:794–795
https://doi.org/10.1038/s41440-023-01542-1

COMMENT

How can endocan be used as a specific biomarker of endothelial dysfunction in hypertension?

Yoshitaka Hirooka[1]

Keywords Endothelium · Nitric oxide · Inflammation · Biomarker · Endocan

Received: 26 October 2023 / Revised: 9 November 2023 / Accepted: 14 November 2023 / Published online: 19 December 2023

Endothelial dysfunction occurs in patients with hypertension even at an early stage [1], although it remains unknown whether it is a cause or consequence [1]. Nitric oxide (NO) production is reduced because of the injured endothelium in association with damaged endothelium NO synthase, increased oxidative stress, and/or an increase in the endogenous NO synthase inhibitor asymmetric dimethylarginine [1]. Moreover, reactive oxygen species generation is increased, further enhancing oxidative stress [1, 2]. Activation of the sympathetic nervous system and inflammatory changes also affect endothelial function in hypertension [1, 2]. In addition, chronic low levels of inflammation have an important role in the pathogenesis of hypertension [3]. Several studies suggest the potential application of endocan, a soluble dermatan sulfate proteoglycan mainly secreted by activated endothelium, as a marker of endothelial dysfunction in patients with hypertension [4].

Endocan secretion is controlled by proinflammatory cytokines such as tumor necrosis factor-α and interleukin-1β [5]. It is encoded by the endothelial cell-specific molecule-1 gene and was discovered in human umbilical vein endothelial cells [5]. Endocan increases with inflammation, suggesting that it is increased not only in hypertension, but also in other diseases [4]. It can promote the expression of cellular adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1), which leads to atherosclerotic plaque formation [4, 5] (Fig. 1). Thus, increased endocan levels may be important for atherosclerotic plaque formation with hypertension. Indeed, some studies report that carotid intima-media thickness and high sensitivity C-reactive protein levels are correlated with increased endocan levels [4].

In this issue of the journal, Behnoush et al performed a systematic review and meta-analysis to evaluate whether the endocan level is a possible biomarker of endothelial dysfunction in hypertensive patients [6]. After searching the literature on the role of endocan as a biomarker of hypertension, they analyzed 20 studies with 3130 participants. They conclude that circulating endocan levels are significantly higher in hypertensive patients than in normotensive controls, and suggest that endothelial dysfunction is responsible for the elevated endocan levels in hypertensive individuals due to the nature of endocan.

Few studies, however, have examined endothelial function on the basis of flow-mediated vasodilation (FMD) values or other qualifying NO levels. One study in which FMD and asymmetric dimethylarginine were measured in patients with autosomal dominant polycystic kidney disease found that endocan levels were elevated in those patients regardless of the presence of hypertension, although FMD levels were lower in patients with hypertension [7]. Another study examining FMD in patients with obstructive sleep apnea syndrome, which is sometimes associated with hypertension [8], found that serum endocan levels were higher in these patients and the serum endocan level was strongly correlated with FMD [8]. Another important issue is that increases in endocan levels reflect inflammation. Although a low level of inflammation is an important factor in hypertension as well as other cardiovascular diseases, endocan levels increase in many other diseases and as described, the underlying mechanisms might differ [6].

Endocan levels may also reflect the duration of hypertension, severity, and related comorbidities such as diabetes and chronic kidney disease, and the therapeutic benefits [4]. Thus, many factors influence circulating endocan levels in hypertensive patients with these comorbidities as well as

✉ Yoshitaka Hirooka
hyoshi@iuhw.ac.jp

[1] Department of Cardiovascular Medicine, International University of Health and Welfare Graduate School of Medicine, Okawa City, Fukuoka, Japan

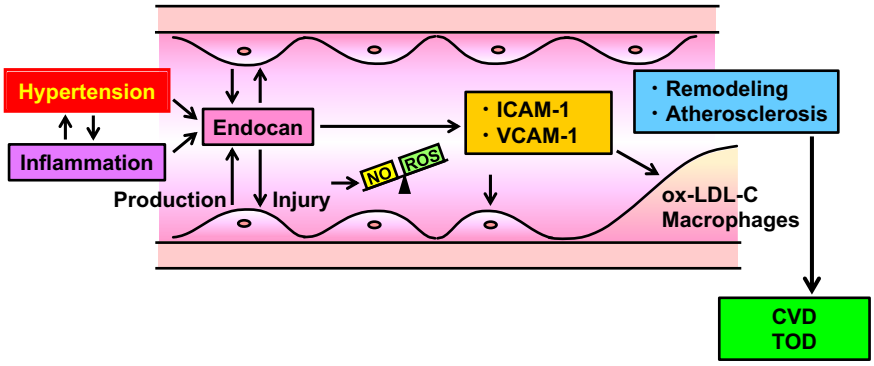

Fig. 1 Scheme for presenting effects of endocan and related endothelial dysfunction leading to arterial remodeling and atherosclerotic changes from hypertension and/or inflammation. NO nitric oxide, ROS reactive oxygen species, ox-LDL-C oxidative LDL-cholesterol, TOD target organ damage, CVD cardiovascular disease

other inflammatory diseases, such as autoimmune diseases and cancers [4, 6]. In fact, many papers describe increased endocan levels in patients with cancer [9]. Endocan could be a possible target for cancer therapy [9]. It would be interesting to examine endocan levels after treating hypertension in patients with cancer.

Another meta-analysis paper demonstrated that serum endocan levels are significantly increased in a population with cardiovascular disease [10], although the analysis was not specific for endothelial function and hypertension. These authors propose that a high serum endocan level is a risk factor for cardiovascular disease and suggest the importance of monitoring serum endocan preceding the occurrence and development of disease. Injury, activation, and disorder of endothelial cells are involved in the occurrence and development of hypertension. In this paper, they describe hypertension as a cardiovascular disease. They also report that inflammation and atherosclerotic processes, target organ damage, and antihypertensive treatment reduced serum endocan levels in naïve hypertensive patients. If this is validated, it would be useful for risk stratification and therapeutic monitoring.

In conclusion, endocan may be useful as a biomarker for assessing endothelial function in patients with hypertension, including the many aspects of the pathophysiological status, including inflammatory and atherosclerotic processes, as shown in the Figure. The endothelium is activated and/or damaged by hypertension and/or inflammation. Subsequent processes would lead to vascular remodeling for the development of hypertension and atherosclerotic plaque formation because of increases in adhesion molecules such as ICAM-1 and VCAM-1, and thereby monocyte migration to the intima transforming to macrophages. Macrophages and oxidative LDL-cholesterol then accelerate unstable plaque formation, finally causing target organ damage and cardiovascular disease. In this serial process, therefore, other inflammatory markers need to be examined to evaluate the characteristics of inflammation affecting the disease status of hypertension for risk stratification and therapeutic monitoring. Additional prospective studies are still needed to validate the importance of the serum endocan level in patients with hypertension.

Compliance with ethical standards

Conflict of interest The author declares no competing interests.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

1. Maruhashi T, Higashi Y. Cardiovascular risk in patients receiving antihypertensive drug treatment from the perspective of endothelial function. Hypertens Res. 2022;45:1322–33.
2. Kishi T, Hirooka Y, Konno S, Sunagawa K. Angiotensin II receptor blockers improve endothelial dysfunction associated with sympathetic hyperactivity in metabolic syndrome. J Hypertens. 2012;30:1646–55.
3. Hirooka Y. Sympathetic activation in hypertension: importance of the central nervous system. Am J Hypertens. 2020;33:914–26.
4. Chen J, Jiang L, Yu X-H, Hu M, Zhang Y-K, Liu X, et al. Endocan: a key player of cardiovascular disease. Front Cardiovasc Med. 2022;8:798699.
5. Béchard D, Gentina T, Delehedde M, Scherpereel A, Lyon M, Aumercier M, et al. Endocan is a novel chondroitin sulfate/dermatan sulfate proteoglycan that promotes hepatocyte growth factor/scatter factor mitogenic activity. J Biol Chem. 2001;276:48341–9.
6. Behnoush AH, Khalaji A, Bahiraie P, Alehossein P, Shobeiri P, Peisepar M, et al. Endocan as a marker of endothelial dysfunction in hypertension: a systematic review and meta-analysis. Hypertens Res. 2023;46:2388–99. https://doi.org/10.1038/s41440-023-01402-y
7. Ekinci I, Buyukkaba M, Cinar A, Tunc M, Cebeci E, Gursu M, et al. Endothelial dysfunction and atherosclerosis in patients with autosomal polycystic kidney disease. Cureus. 2021;13:e13561.
8. Kanbay A, Ceylan E, Köseglu HI, Caliskan M, Takir M, Tulu S, et al. Endocan: a novel predictor of endothelial dysfunction in obstructive sleep apnea syndrome. Clin Respir J. 2018;12:84–90.
9. Zhao T, Kecheng YK, Zhao X, Hu X, Zhu J, Wang Y, et al. The higher serum endocan levels may be a risk factor for the onset of cardiovascular disease: a meta-analysis. Medicine. 2018;97:49.
10. Sarrazin S, Adam E, Lyon M, Depontieu F, Motte V, Landolfi C, et al. Endocan or edndothelial cell specific molecule-1 (ESM-1): a potential novel endothelial cell marker and a new target for cancer therapy. Biochimica et Biophysica Acta. 2006;1765:25–37.