Erciyes Med J 2021; 43(3): 233–6 • DOI: 10.14744/etd.2020.09699
REVIEW – OPEN ACCESS

An Overview of Clinical Studies on Endocan and Cardiovascular Disease

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ABSTRACT

Endothelial dysfunction is a catastrophic condition caused by disruption of the equilibrium between vasodilatation and vasoconstriction. Endocan is a proteoglycan derived from vascular endothelium. Endocan can interact with biologically active molecules, and these active molecules are essential for the balance of many biological functions, including cell adhesion, migration, proliferation, and new blood vessel formation. Increased endocan levels cause atherosclerosis in hypertension and coronary artery disease. We aimed to present a review of the biological functions of the endocan and the prevention of atherosclerosis.

Keywords: Atherosclerosis, endocan, endothelial dysfunction

INTRODUCTION

Inflammatory cells play an important role in the development of atheroma and plaque formation, which are atherosclerotic processes (1). Systemic inflammation parameters may lead to cardiac disease (2). The endothelium controls vascular tone and hemostasis through endothelial vasoactive mediators (3). In contrast, endothelial function is adversely affected by systemic inflammation (4).

Endocan acts on mechanisms such as endothelial leukocyte uptake, adhesion, and transport required for vascular activation. At the same time, the only known function of the endocan is the binding of (soluble) intercellular adhesion molecule 1 (ICAM–1) to leukocyte integrin lymphocyte function–associated antigen 1 (LFA–1) (CD11a/CD18), which prevents dose–specific binding of LFA–1. ICAM–1 (endothelial binding partner of LFA–1) can inhibit cell to cell contact, trigger migration of circulating mononuclear cells to inflammatory sites. These molecules regulate the adherence of leukocytes to the endothelium and their migration to inflammatory sites (5). The relationship between ICAM–1 and LFA–1 also affects the binding of cytotoxic lymphocytes and natural killer cells to inflammatory sites. Recently, it has been claimed that the endocan inhibits the dose–dependent migration of lethal cells naturally present in the vascular system (6).

Therefore, endocan may cause inflammatory and vasculoprotective effects and involve in the formation of atherosclerosis. It has been reported that serum endocan with other biomarkers is a significant marker for certain cancers, systemic inflammation, and other cardiovascular diseases (CVDs) (7). Serum endocan levels have an indirect effect on the severity and outcome of the disease (8, 9). Association of tumor progression and inflammatory diseases with increased endocan levels has been demonstrated in various studies. Endocan, as an important indicator of endothelial dysfunction, has been identified by the last epidemiological studies (10).

Endocan increases pro–inflammatory cytokine, microvascular permeability, and leukocyte migration by an effect on the endothelial cells. Endocan induces atherogenesis by stimulating vascular smooth muscle cell proliferation and migration (11). Endocan affects vascular diseases, organ–specific inflammation, and endothelium–dependent pathological disorders (12). A recent study found that patients with acute coronary syndrome (ACS) have higher endocan levels (13). However, there was not a correlation between plaque burden and endocan in this study (13).

In this review, we aimed to investigate endocan in CVD for the reason of a promising marker for CVD.

Endocan and Cardiovascular (CV) Risk Factors

Endocan mediates proliferation, migration, and neointima formation of vascular smooth muscle cells (6). Hypertension (HT) and endothelial dysfunction are interconnected and the underlying mechanism is increased inflammation. Stress may damage the endothelium in hypertensive patients. Epidemiological data have shown an association between inflammatory markers and HT (3). A positive association between inflammatory plasma cells, apoptosis molecules, and target organ damage has been found in hypertensive patients (14).

Cite this article as:
Aşkın L, Tanrıverdi O. An Overview of Clinical Studies on Endocan and Cardiovascular Disease. Erciyes Med J 2021; 43(3): 233-6.

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Submitted
08.02.2020

Accepted
29.10.2020

Available Online
05.04.2021

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Vascular inflammation contributes to the pathophysiology of HT, and high endocan levels may reflect this underlying inflammation. A recent study investigated higher serum endocan levels in newly diagnosed essential HT patients (15). Besides, serum endocan level is related to carotid intima–media thickness (cIMT) and high sensitivity C–reactive protein (hsCRP) level (15). In another study, amlodipine and valsartan levels in 37 newly diagnosed HT patients showed that both amlodipine and valsartan decreased endocan levels (16). Tadzic et al. (17) evaluated the effect of low blood pressure (BP) on the endocan. Decreased endocan levels are associated with low BP, insufficiency of adhesion leukocytes, and lower risk of atherosclerosis.

Çelik et al. (16) showed that amlodipine and valsartan decrease endocan levels in newly diagnosed hypertensive patients. The anti–inflammatory effects of the two drugs may contribute positively to the vascular system. Serum endocan level monitoring may be an essential step forward in predicting the occurrence and development of HT, coronary artery disease, and coronary slow flow (CSF) (18).

Dyslipidemia is a major cardiac risk factor and associated with endothelial dysfunction. There are no previous data about the relationship between endocan and dyslipidemia. However, lipid–lowering therapy improves endothelial function in patients at increased risk of vascular disease (19).

Early atherosclerosis is the most cause of increased morbidity and mortality in chronic kidney disease (CKD). Endothelial dysfunction is an important cause of increased CVD risk in patients with CKD. Yılmaz et al. (20) concluded that endocan values were inversely related to estimated glomerular filtration rate in patients with CKD. Endocan levels affect all–cause deaths and CVD events in CKD patients, regardless of traditional risk factors. The addition of endocan to a prediction model based on standard and non–traditional risk factors improves the prediction of fatal and non–fatal CKD events (20).

Chew et al. (21) demonstrated that plasma endocan expression was higher in pregnant hypertensive women. Endocan expression was higher in almost all hypertensive groups. Endocan release increased in conditions such as preeclampsia, low birth weight, and prematurity (21).

Pawlak et al. (22) demonstrated that plasma endocan was significantly increased in non–dialyzed CKD patients with CV history and independently associated with sICAM–1 and soluble vascular cell adhesion molecule–1 (sVCAM–1) levels. The endocan–mediated pathway affects cellular adhesion molecules and plays an active role in conditions such as uremia, inflammation, and endothelial activation.

Increased endocan levels are significantly related to CSF. It is also positively associated with hsCRP and other inflammatory markers such as white blood cell count (WBC) and neutrophils. The results highlight that the higher endocan levels may indicate endothelial dysfunction with increased inflammatory response in CSF. Elevated endocan levels are indicative of the dysfunction of endothelial cells (23).

Ye et al. (24) found an independent association between serum endocan concentration and CSF. Endocan may be used to predict the presence and severity of CSF. Endocan may be a novel biomarker as a therapeutic target for patients unsuitable for conventional strategies such as coronary bypass surgery or percutaneous intervention (25).

Serum endocan, asymmetric dimethylarginine (ADMA), and transforming growth factor–β (TGF–β) levels are associated with endothelial dysfunction in subclinical hypothyroidism (26). In particular, ADMA was correlated with both endocan and hs–CRP levels. These findings are suggestive for increased risk of endothelial dysfunction and subsequent development of atherosclerosis in patients with subclinical hypothyroidism. In obstructive sleep apnea (OSAS), the plasma tumor necrosis factor (TNF) receptor superfamily member 11b (TNFRSF11B) has higher discriminatory accuracy than plasma endocan (27). Endocan and thrombomodulin are two biomarkers released from the endothelium that is associated with dysfunction. Baysal et al. (28) investigated the relationship of isolated coronary artery ectasia (CAE) with these markers. The effect of the cytokine on endocan production and the view of endocan as an inflammatory marker supports the positive correlation of endocan and TNF–α (29).

Chronic lead exposure causes diastolic dysfunction. By a similar mechanism, serum endocan level for this population may be a valuable marker for diastolic dysfunction (30). Zhao et al. (31) demonstrated that attenuated monocrotaline miR–181a/b overexpression causes high mortality, pulmonary HT, right ventricular remodeling, endocan activation, and in vivo inflammation. The luciferase reporter assay confirms that miR–181a/b interacts directly with the endocan. Furthermore, in vitro results confirm the reduction of miR–181a/b in TNF–α–induced inflammatory conditions by reduction of the endocan (31).

A recent study showed that patients with chronic heart failure (CHF) have elevated endocan levels and endocan levels are associated with the prognosis of CHF (32). Endocan has emerged as an independent prognostic marker of mortality and hospitalization in CHF patients. In conclusion, endocan may serve as a simple marker for better risk classification in the CHF population (32).

Menon et al. (33) showed that endocan may cause impaired ventricular function in the postpartum period. Qiu et al. (34) demonstrated the linear relationship between admission glucose levels and endocan levels in ST–elevation myocardial infarction (STEMI). An endocan level >1.01 ng/mL is an independent predictor of major cardiac adverse events (MACEs). Findings may contribute to understanding the pathogenesis of endothelial dysfunction in STEMI patients with stress hyperglycemia. Plasma endocan levels help determine isolated coronary ectasia and affect the pathogenesis of isolated coronary ectasia (35).

Endocan is a predictor of MACE and its prognostic value is comparable to the thrombolysis in myocardial infarction (TIMI) risk score. The TIMI risk score is useful for the rapid assessment of patients with ACS. However, endocan, as an early complement biomarker, helps assess the prognosis for the TIMI risk score (36).

Higher endocan levels may cause adverse CV outcomes and related to higher SYNTAX scores in STEMI patients (37). Endocan may be useful as an indicator of the prognosis of patients with STEMI.

Serum endocan levels are higher in women with polycystic ovary syndrome (PCOS) and independently associated with cIMT in PCOS. For this reason, endocan may indicate increased CV risk in PCOS (38). Efe et al. (39) aimed to help to understand the pathogenesis of cardiac syndrome X better. Higher endocan levels may be

Table 1. Characteristics of studies

Reference	Sample size	Population type	Inflammatory marker correlations
Balta et al. (2), 2014	32	Psoriasis	Endocan, CRP
Karaman et al. (3), 2013	46	HT	Von Willebrand factor, neutrophil to lymphocyte ratio
Balta et al. (5), 2013	53	CAE	WBC, neutrophil to lymphocyte ratio
Balta et al. (9), 2013	33	Behçet	Endocan, CRP, erythrocyte sedimentation rate
Balta et al. (10), 2015	29	Psoriasis vulgaris	Endocan, hsCRP
Kose et al. (13), 2015	53	ACS	Endocan, hsCRP
Balta et al. (15), 2014	18	HT	Endocan, hsCRP
Çelik et al. (16), 2014	37	HT	Endocan, hsCRP
Tadzic et al. (17), 2013	24	HT	sICAM–1 and sVCAM–1
Yılmaz et al. (20), 2014	251	CKD	Pentraxin 3 and hsCRP
Pawlak et al. (22), 2015	53	CKD	hsCRP, interleukin-6, TNF-α
Kundi et al. (23), 2017	88	CSF	Endocan, hsCRP
Emet et al. (25), 2017	27	Stable angına with CTO	Endocan, hsCRP
Arpaci et al. (26), 2016	45	Subclinical hypothyroidism	ADMA, endocan, TGF-β
Wena et al. (27), 2019	120	OSAS	TNFRSF11B, endocan
Baysal et al. (28), 2019	32	CAE	Endocan, thrombomodulin

CRP: C–reactive protein; HT: Hypertension; CAE: Coronary artery ectasia; WBC: White blood count; TGF-β: Transforming growth factor-β; TNF-α: Tumor necrosis factor-α; hsCRP: High sensitivity C–reactive protein; ACS: Acute coronary syndrome; sICAM-1: Soluble intercellular adhesion molecule 1; sVCAM-1: Soluble vascular cell adhesion molecule-1; CKD: Chronic kidney disease; CSF: Coronary slow flow; ADMA: Asymmetric dimethylarginine; OSAS: Obstructive sleep apnea; CAE: Coronary artery ectasia; TNFRSF11B: Tumor necrosis factor receptor superfamily member 11b

a good predictor of microvascular disease, and further studies may provide a closer follow–up of patients with cardiac syndrome X (39).

Musialowska et al. (40) reported that well–controlled primary HT had higher endocan plasma concentration than controls. Inflammatory marker correlations and the other characteristics of studies are summarized in Table 1.

In summary, studies show that endocan may have a functional role in endothelium–dependent pathological disorders. Whether endocan levels could become a treatment target merits further investigation. In diseases such as CKD, kidney transplant rejection, tumor progression, HT, diabetes, and dyslipidemia, significant increased endocan levels have been observed. Endocan is a promising inflammatory marker in CVD. More clinical applications are needed to delineate the significance of the endocan.

CONCLUSION

Endocan is a promising new inflammatory marker in CVD. Serum endocan level monitoring may be an important step forward in predicting the occurrence and development of CVD, and serial measurements may shed light on the effect of therapy on endothelial functions. There are limited studies about the prognostic impact of endocan levels and comprehensive studies are needed to understand endocan.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – LA, OT; Design – LA, OT; Supervision – LA, OT; Data Collection and/or Processing – LA, OT; Analysis and/or Interpretation – LA; Literature Search – LA, OT; Writing – LA; Critical Reviews – LA, OT.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

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