Role of Endocan in Cardiovascular disorders

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Abstract

Endocan, which was found two decades ago, continues to be a fascinating indicator of inflammation. Endothelial cells release the soluble dermatan sulphate proteoglycan known as endocan. Particularly in hepatocytes, tissues connected to the accelerated proliferation, it is seen to express itself kidneys, lungs, etc. Numerous cardiometabolic conditions that are closely linked to inflammation, such as type 2 diabetes, hypertension, atherosclerotic cardiovascular disease, kidney disease, obesity, polycystic ovary syndrome, metabolic syndrome, non-alcoholic fatty liver disease, etc., have been studied in relation to endocan.

Keywords: • Atherosclerosis • Endocan • Endothelial dysfunction• Inflammation • Cardiovascular disease

Introduction

Endocan is a new proteoglycan with a low molecular weight that was identified twenty years ago (formerly known as Endothelial-Specific Molecule, or ESM-1). Since endothelial cells are the primary site of its secretion, it is regarded as a sign of endothelial dysfunction.

Structure of endocan

Endocan differs from numerous other Dermatan Sulphate (DS) proteoglycans in a number of respects, including size: It can be detected in circulation because it has the following characteristics: it is a DS with a low molecular weight (roughly 50 kDa); it is a soluble, secreted DS that is not linked to the cell membrane or extracellular matrix; this allows endocan to act at distant cells; it has only one single short DS chain rather than multiple glycosaminoglycan chains; and it has a higher content of disulphated disacchari. In humans, endocan is encoded by a gene known as ESM-1. The protein core of endocan, which has 165 amino acids, is composed of two distinct domains: the N-terminal cysteine-rich (110 amino acids) and cysteine-free (55 amino acids) domains. The latter is split into three sections: the C-terminal area, which is at the end of the cysteine-free domain, the phenylalanine-rich region, which is in the centre of the cysteine-free domain, and the epidermal growth factor-like region, which is closest to the cysteine-rich domain. Through post-translational modification, serine 137 connects the core protein to the chain of glycosaminoglycan.

Secretion and expression of endocan

Although endothelial cells release endocan, it is also found in tissues with increased proliferation, including hepatocytes, bronchial epithelium, neurons, glandular, and kidney tissue.In patients with severesepsis, endocan expression has been found to be greater in prior investigations. Endocan is overexpressed in cancer cells as well, suggesting that this proteoglycan contributes to the formation of tumours, which may partially account for its increased expression in various carcinomas. Numerous proinflammatory mediators, including Tumour Necrosis Factor-alpha (TNF-alpha), interleukin-1, fibroblast growth factor-2, and Vascular Endothelial Growth Factor-A (VEGF-A), stimulate the release of endocan. Several mitogens, including phorbol ester and retinoic acid, have also been found to increase in vivo endocan expression in adipocytes. Conversely, interferon- reduces the expression of endocan.

Mechanism of action of endocan

Even in the early phases of atherosclerosis, endocan is important . Endocan demonstrates endothelial dysfunction, which includes a number of essential physiological effects such modulating leukocyte migration, leukocyte adhesion, and vascular smooth-muscle cell proliferation. Endocan itself can cause the endothelium to produce a number of cytokines that force leukocytes to migrate and increase blood vessel permeability.

Nuclear Factor kappa B (NF-B) and Mitogen-Activated Protein Kinase (MAPK) signalling pathways are responsible for endocan's proinflammatory effects. Intercellular Adhesion Molecule (ICAM-1), Vascular Cell Adhesion Molecule (VCAM-1), and E-Selectin expression is increased as a result of these events, favouring leukocyte migration and adherence to endothelial cells.

A biomarker called VEGF-A promotes endocan production and makes endocan more active on cell adhesion molecules by attaching to its receptor. Via the Protein Kinase C (PKC)/nuclear factor kappa B (NF-B) pathway, VEGF-A increases endocan mRNA and protein production in endothelium, but Phosphoinositide 3-Kinase (PI3K) inhibits this activity. The permeability of blood arteries is enhanced by VEGF-A.

Endocan and obesity

Cardiometabolic diseases have obesity as a known risk factor. Numerous pro-inflammatory cytokines and adipokines are secreted by adipose tissue. Since obesity is thought to be a condition linked to the start of atherogenesis and Atherosclerotic Cardiovascular Disease (ASCVD) and low-grade, persistent, chronic inflammation ,The evidence that exists about the link between endocan and obesity, however, is debatable. While some studies have demonstrated higher endocan levels in obesity and a positive correlation between anthropometric measurements of both overall obesity (i.e., Body Mass Index (BMI) and abdominal obesity (i.e., Waist Circumference (WC), others have revealed the opposite, i.e., lower endocan levels in obesity and a detrimental association with the anthropometric indices. These disagreements may be related to the many ethnic groups examined, the phenotypes of adiposity, the duration and severity of obesity, and the population sample size. Age and gender distribution varied between the examined groups, which could also account for these differences.

The first study to look at endocan's function in obesity was done by Wellner et al. They demonstrated enhanced adipocyte endocan expression and hypothesised that endocan might play a role in controlling the inflammatory response. Accordingly, after inducing proinflammatory mediators in the placenta, endocan expression was found to be higher in a group of pregnant women with obesity and gestational diabetes mellitus (n=40) compared to pregnant women (n=10) with normal glucose tolerance.

Endocan and polycystic ovary syndrome

A metabolic condition called Polycystic Ovary Syndrome (PCOS) has IR as its primary underlying pathophysiologic mechanism. Endothelial

dysfunction is seen in PCOS in addition to metabolic alterations (such as central obesity, dyslipidemia, dysglycemia, and hypertension), which suggests that women with PCOS are at a higher risk of Cardiovascular Disease (CVD). It typically affects premenopausal women. There are few studies that looked into the connection between endocan and PCOS, and inconsistent findings have been found. The PCOS group displayed greater serum endocan levels in a cross-sectional research that comprised 88 women of reproductive age with PCOS and 87 controls who were age and BMI matched. However, normal-weight PCOS patients had greater serum endocan levels than overweight/obese PCOS women when grouped based on baseline BMI. Additionally, it was discovered that endocan had a favourable correlation with HDL-c levels but a negative correlation with BMI and CRP.

Endocan and metabolic syndrome

One of the earliest and most important pathophysiologic pathways linked to the onset, progression, and complications of ASCVD-related Metabolic Syndrome (MetS) is endothelial dysfunction. According to Iwa 'nczyk et al., people with MetS (n=34) had greater serum endocan levels than people without MetS (n=56). The findings in a paediatric group were similar. In more detail, Halici et al. found that children with MetS (n=30) had endocan levels that were nearly three times higher than those of children without MetS (n=30). Another recent study found that although the difference did not achieve statistical significance, median circulating endocan concentrations were greater in persons with prediabetes (n=59) than in the control group (n=117). Contrarily, Arman et al. found that people with prediabetes (n=42) had lower levels of circulating endocan than did healthy controls (n=42). In addition, MetS participants (n=44) have lower levels of circulating endocan than MetS-free people (n=26), according to Boyuk et al.

Endocan and non-alcoholic fatty liver disease

Circulating endocan levels in non-alcoholic fatty liver disease: As a hepatic manifestation of MetS, Non-Alcoholic Fatty Liver Disease (NAFLD) is characterised by increased levels of free fatty acids entering the liver, increases in lipid accumulation, IR, oxidative stress, and inflammation. It has been demonstrated that NAFLD is a standalone cardiovascular risk factor. Hepatocyte lesions have the potential to increase collagen formation, trigger apoptosis in hepatocytes, and ultimately result in fibrosis, cirrhosis, and hepatocellular cancer if they are left untreated.Regarding the function of endocan in NAFLD, conflicting findings have been reported .In contrast to people with NAFLD who had no coronary artery disease (n=11), patients with NAFLD and CAD (n=66) had higher levels of endocan in the blood. The fatty liver index was used to diagnose NAFLD, and endocan levels were shown to be greater in this group (n=147) than in the group without liver disease (n=64).

Circulating endocan levels in liver fibrosis: According to a recent study, patients with NAFLD (as identified by the fatty liver index) had a median endocan level of 38.8 (21.6 ng/L-89.5 ng/L). According to the BARD score, the median endocan level in patients with advanced fibrosis was 44.2 (22.8 ng/L-92.7 ng/L), whereas it was 27.8 (17.6 ng/L-40.9 ng/L) in healthy controls. This suggests that an increase in serum endocan levels may be linked to the progression of liver disease. Additionally, by including additional factors like TG, age, gender, and antihypertensive therapy in the developed prognostic model, the diagnostic precision of endocan for liver fibrosis was improved. This model showed excellent discriminatory capability (Area Under the Curve (AUC) = 0.840) for advanced fibrosis, with sensitivity and specificity of 72.41% and 86.36%, respectively, in contrast to the poor discriminatory capability of endocan for liver fibrosis as a single.

Endocan and Type 2 diabetes mellitus

Circulating Endocan Levels in Type 2 Diabetes Mellitus: It was discovered that serum endocan levels were considerably greater in the T2DM cohort compared to the prediabetes and control groups in an earlier observational study that included 59 patients with prediabetes, 102 patients with T2DM, and 117 controls. Notably, a multivariate logistic ordinal regression analysis found that a one-unit increase in serum endocan was associated with a two-fold increase in the likelihood of having higher HbA1c levels, indicating a link between this new endothelial dysfunction biomarker and poor glycemic control in T2DM.

Relationship between endocan, endothelial dysfunction, and subclinical atherosclerosis in type 2 diabetes mellitus: Circulating endocan levels are higher in subjects with T2DM and concurrent endothelial dysfunction compared to those with baseline T2DM without endothelial dysfunction, demonstrating that endocan is an independent predictor of endothelial dysfunction, significantly increasing the corresponding odds by almost 46%, according to a previously published case-control study involving 88 patients with T2DM and 88 healthy controls. In a different case-control research, 28 healthy controls and 69 T2DM patients with and without subclinical atherosclerosis were included.

Endocan and microvascular complications of type 2 diabetes mellitus: Data from recently released observational studies point to a strong connection between endocan levels and T2DM microvascular problems. In a previous case-control study, it was discovered that: patients with T2DM and DN had significantly higher circulating endocan levels compared to healthy controls, and patients with T2DM and DN also had significantly higher circulating endocan levels than subjects without underlying DN, suggesting an emerging role of endocan in several different conditions. The Code of Ethics is a tool that aids. The Urine Albumin-Creatinine Ratio (UACR) had a significant negative bivariate correlation with serum endocan levels, and patients with macroalbuminuria had lower circulating endocan levels than those with normoalbuminuria and microalbuminuria, according to results of another observational study involving 137 patients with T2DM and normal baseline renal function. Last but not least, some data also points to a potential function for endocan in the aetiology of Diabetic Retinopathy (DR). Analysis of vitreous fluid samples from 44 patients with T2DM proliferative DR and 29 people without underlying T2DM found that endocan levels in patients with DR were considerably greater than in non-diabetic subjects.

Endocan and macrovascular complications of type 2 diabetes mellitus: To present, only one study has examined the potential contribution of endocan in the development of macrovascular problems in T2DM patients. In particular, it was shown in a previous cross-sectional study from China that included 33 normotensive controls, 72 patients with T2DM, 38 of whom had a recent history of acute myocardial infarction but no other CVD, and that: (1) subjects with underlying T2DM had significantly higher serum endocan levels; and (2) subjects with T2DM and recent myocardial infarction had significantly higher serum endocan levels than subjects with T2DM and no history of such events.

Endocan and arterial hypertension

Circulating endocan levels in arterial hypertension: Serum endocan levels were significantly higher in the primary arterial Hypertension (HTN) group in a previous cross-sectional study that included 18 patients with the condition and 23 matched, normotensive controls. The HTN group also showed a significant, positive correlation with markers of subclinical atherosclerosis (such as cIMT) and inflammation (such as hsCRP). Another cross-sectional investigation with 61 newly diagnosed HTN patients and 30 healthy controls revealed comparable findings, demonstrating a positive, significant connection between endocan levels and both cIMT and systolic blood pressure. Another cross-sectional study with 67 patients with newly diagnosed essential HTN and 70 healthy controls found that endocan levels were significantly higher in hypertensive subjects and were positively correlated with the aortic elastic properties measured by echocardiography, specifically aortic strain and aortic distensibility, further confirming the close association between endocan levels and target-organ damage in HTN.

Relationship between endocan levels and atherosclerotic cardiovascular disease in subjects with hypertension: An earlier cross-sectional investigation with 190 hypertensive participants that evaluated them for potential coronary artery disease (CAD) using coronary angiography found that those who had verified CAD had considerably greater levels of circulating endocan . Endocan caused a two-fold, statistically significant increase in the likelihood of having CAD, demonstrating its role as an independent predictor for its occurrence.

Endocan and atherosclerotic cardiovascular disease

Circulating endocan levels in coronary artery disease: High serum endocan levels have been shown to be an independent predictor of incomplete ST-Segment Resolution (STR) among people with a history of a recent ST-Segment Elevation Myocardial Infarction (STEMI), serving as a marker of insufficient myocardial perfusion after primary percutaneous coronary

intervention and, consequently, of worse clinical prognosis. Another pertinent investigation that included STEMI patients receiving primary percutaneous coronary intervention produced results that were comparable, demonstrating that greater circulating endocan levels were an independent predictor of the occurrence of the no-reflow phenomena and decreased myocardial perfusion.

Circulating endocan levels and cerebrovascular disease: Higher endocan levels were linked to a significant increase in the odds for a composite endpoint of death or major disability within the first months following the occurrence of the stroke, even though the increase in the odds of death was non-significant after adjusting for confounding factors in another cross-sectional study recruiting patients with a recent acute ischemic stroke. Additionally, studies have indicated that patients with major artery atherosclerotic stroke have greater endocan levels than controls.

Circulating Endocan Levels and Heart Failure: Even in the field of Heart Failure (HF), endocan has become a novel, prognostic biomarker. Among people with chronic, stable HF, an increase in circulating endocan levels by 1 ng/mL was significantly associated with a 47% increase in the risk of HF-related mortality or hospitalisation requiring inotropic support.

The impact of cardiometabolic-targeted therapies on endocan levels: Unfortunately, there is a dearth of information on how cardiometabolic-targeted medications affect the amounts of circulating endocan. A prior randomised trial in the field of hypertension that included 37 subjects with newly diagnosed essential hypertension showed that 3-month treatment with either valsartan or amlodipine led to a significant decrease in circulating endocan levels, with amlodipine producing a greater numerical decrease. It's important to highlight that there was no connection between the change in blood pressure and the amount of circulating endocan. 63 participants were recruited for a previous randomised experiment in the field of ASCVD.patients underwent percutaneous coronary intervention for a recent acute myocardial infarction and were given either a high-intensity atorvastatin or rosuvastatin therapy,showed that rosuvastatin, but not atorvastatin, caused a reduction in total cholesterol following a 4-week treatment.endocan levels in the blood have significantly decreased .

Future Perspectives

Endocan, which was found two decades ago, continues to be a fascinating indicator of inflammation. Endocan is being researched in numerous inflammation-related cardiometabolic diseases, including obesity, polycystic ovary syndrome, metabolic syndrome, non-alcoholic fatty liver disease, type 2 diabetes mellitus, hypertension, atherosclerotic cardiovascular disease, kidney disease, etc. Although there are some contentious findings, the disparities may be explained by the diverse ethnic groups that were researched, the age and gender distribution, the forms of adiposity, the duration and severity of obesity, and the population sample size.

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