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ARTICLE

Elevated endostatin is associated with hypertension treatment, elevated high sensitivity CRP, increased waist-hip ratio, and attenuated kidney function, but not with age, in a middle-aged population

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Abstract

Circulating endostatin has been linked to increased mortality, cardiovascular comorbidities, and renal impairment. However, its role as a cardiovascular risk marker in the general population remains largely unexplored. This study investigates the association between plasma endostatin and atherosclerosis, inflammation, and kidney function in a cohort of 5,026 randomly selected middle-aged individuals from the Swedish CArdioPulmonary bioImage Study (SCAPIS). Plasma levels of endostatin, C-reactive protein (CRP), HbA1c, lipids, and creatinine were analyzed, and their associations with atherosclerosis and related markers were assessed. Coronary artery atherosclerosis was evaluated using coronary computed tomography. Blood pressure, body mass index, and waist circumference were measured, and medication use for diabetes, hyperlipidemia, and hypertension was recorded. Smoking habits were also documented. The following main results were significantly associated with endostatin. Severe coronary atherosclerosis was positively associated in men. Being on hypertensive medication or not, as reported by the participants at the interview at study inclusion, was significantly associated with endostatin. Hypertensive medication increased from 12% to 26% from the lowest to the highest quartile of endostatin. Waist circumference was positively associated, where endostatin increases, on average, 0.21SD for a 1SD increase of waist circumference. Kidney function, measured as eGFR, was negatively associated, where endostatin decreases, on average, 0.22SD for a 1SD increase in eGFR. Elevated endostatin levels were associated with advanced coronary atherosclerosis in men, antihypertensive treatment, systemic inflammation (increased CRP), increased waist circumference, and impaired kidney function (lower eGFR).

Key words: endostatin; glomerular filtration rate; cardiovascular disease; atherosclerosis.

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Introduction

Endostatin is a 22 kDa proteolytic fragment of type XVIII collagen.[1] Human collagen type XVIII consists of an N-terminal region with multiple splice variants, a central triple-helical domain, and a C-terminal non-collagenous domain, from which endostatin is derived.[2] Endostatin is well known for its role in angiogenesis regulation, the process of new blood vessel formation.[3] While angiogenesis is essential for physiological functions and tissue repair, it can also contribute to tumor progression. Endostatin

regulates angiogenesis via several mechanisms. Endostatin inhibits endothelial proliferation thus reducing the formation of new blood vessels.[4] Endostatin inhibits the migration of endothelial cells to areas where new blood vessels are to be formed.[5] Endostatin interferes with the extracellular matrix formation and induces apoptosis of endothelial cells.[6] Endostatin also has anti-inflammatory properties and anti-tumor growth functions.[7] Finally, endostatin can modulate wound healing and tissue repair.[8] Endostatin plays a crucial role in blood vessel regulation, with potential implications for cancer therapy, wound healing, and diseases linked to abnormal angiogenesis.

Elevated circulating endostatin levels have been identified as a biomarker for vascular and cardiovascular diseases, including diabetes, kidney disorders,[9-11] cerebrovascular disease, and hypertension.[12]

The present study aims to explore associations between plasma endostatin levels and key cardiovascular and kidney disease markers in a middle-aged cohort (50-64 years) to better understand its role in disease progression.

Materials and Methods

Study population and blood samples

SCAPIS is a population-based study conducted at six Swedish University Hospitals, including Linköping University, where this sub-study was conducted.[13] The study included 5,026 participants (2,516 men and 2,510 women), aged 50-64 years. All participants provided written informed consent, and the study was approved by the local Ethics Committee (DNo 2018/478) and the National Ethics Review Authority (DNo 2021-00747). Venous blood samples were collected after an overnight fast using sodium-citrate vacutainer tubes. Plasma was separated by centrifugation (2,500 g, 20 min, room temperature), transferred to new tubes, and stored at -80°C until analysis.

Clinical data

Self-reported data of diagnosis of diabetes, hyperlipidemia, hypertension, rheumatic and cardiovascular disorders, and medications for these conditions were used in the study. Blood lipids and glucose were measured using blood samples after an overnight fast.

Systolic and diastolic blood pressures were measured twice in each arm with an automatic device (Omron M10-IT; Omron Health Care Co., Kyoto, Japan). The mean pressure in the arm with the highest mean blood pressure was registered.

Tobacco smoking was evaluated using a questionnaire asking about current and former cigarette smoking habits, age when starting smoking and years of smoking. Height, weight, waist circumference and waist-hip-ratio were measured by trained health-care staff, and BMI was calculated as weight in kilograms divided by height in meters squared (kg/m^2).

Self-reported data of weight at 20 years, education, employment, and financial problems were collected in a questionnaire.

Laboratory measurements

Endostatin was measured using a commercial ELISA kit (DY1098, R&D Systems, Minneapolis, MN, USA). The endostatin concentrations were the actual values in the citrated plasma without adjusting for the dilution caused by the liquid citrate in the tubes. High-sensitivity CRP (hsCRP) was measured with a quantification limit of 0.15 mg/L.

LDL, HDL, glucose, HbA1c, and creatinine were analyzed at Linköping University Hospital's Clinical Chemistry Department using Cobas c501/701 (Roche Diagnostics, Stockholm, Sweden) and Tosoh G11 HPLC (Sysmex Nordic, Stockholm, Sweden).

eGFR was calculated from the creatinine results using the Lund-Malmö (LM)-rev equation and reported in mL/min/1.73m^2.[14]

Coronary artery atherosclerosis

CT was performed using a dedicated dual-source CT scanner equipped with a Stellar Detector (Somatom Definition Flash, Siemens Medical Solutions). CAC images were obtained using electrocardiogram-gated noncontrast CT imaging at 120 kV. In preparation for CCTA imaging, renal function was assessed and potential contraindications identified to exclude participants for whom administration of contrast media could pose a risk. A β-blocker (metoprolol) and sublingual glyceryl nitrate were given for control of heart rate and dilation of coronary arteries. The contrast medium iohexol (350 mg I/mL; GE Healthcare) was administered at a dose of 325 mg I/kg body weight. CCTA was performed at 100 or 120 kV using five different protocols depending on heart rate, heart rate variability, presence of calcifications, and body weight. Imaging and analyses were performed using a calcium scoring protocol and the calcium content in each coronary artery was measured and summed to produce a total coronary artery calcification score (CACS) according to international standards.[13,15] An Agatston score ≥100 was defined as having coronary artery calcification.

Statistical analysis

Stochastic search variable selection

To explore the associations between endostatin and potential biomarkers, we used Stochastic Search Variable Selection (SSVS), using the R package SSVS.[16-18] SSVS is a Bayesian statistical method that efficiently samples a smaller subset of predictors in a linear regression problem for a given dependent variable. This is done by stochastically iterating over several subsets of predictors to simultaneously sample the predictors and the uncertainty in the regression parameters. The proportion

of times each predictor is included in the model, i.e., the 'posterior inclusion probability' can be used to assess the relative strength for each predictor. The closer the posterior inclusion probability is to 1, the stronger a predictor is to explain the dependent variable. We selected a standard choice of non-informative prior distributions, with a prior inclusion probability of 0.5 for each predictor. As an analogous interpretation[17] of Bayes factors[19] for a model that includes a predictor *j*, M_{j1}, compared to a model that does not, M_{j0}, a posterior inclusion probability above 10/11, corresponding to K=10,[19] was considered as strong evidence for model M_{j1} and we refer to such a predictor *j* as significant. To enable comparison of effect sizes between predictors, we standardized all continuous predictors to zero means and standard deviations of 1.

Bayesian logistic regression

To explore the associations between endostatin and atherosclerotic characteristics, detected by coronary computed tomography angiography (CCTA), we implemented Bayesian logistic regression models using the default non-informative prior distributions in R package UPG.[20] To allow for different associations before and after a certain threshold value of endostatin, we incorporated truncated power splines of order 2 at the threshold value *k*. This means that we added an explanatory variable x^*_j to the already existing predictor x_j for endostatin as $x^*_j (x_j - k)$ if $x_j > k$ and 0 otherwise. Then, we performed Bayesian model selection on a grid of threshold values, where each model was assigned to a specific threshold value on the grid, and the model with the largest probability of the data was considered.

Bayesian zero-inflated negative binomial regression

To explore the associations between CACS and endostatin, we implemented a Bayesian zero-inflated negative binomial (ZINB) regression model using the posterior sampling algorithm with weakly informative priors.[21] The ZINB regression model takes into account zero-inflated count data, which is an inherent feature of our data on CACS with 40% of the values being zero. Associations with endostatin in the Bayesian logistic regression and Bayesian ZINB models were judged as significant if the 95% posterior interval for the corresponding parameter did not include zero.

Results

Baseline data

Baseline data for the cohort is presented in Table 1. The cohort is divided into quartiles based on endostatin levels. The gender distribution was balanced (50.1% male). In the study population, 4.9% had previously diagnosed diabetes, and an additional 2.5% were newly identified cases. Glycemic status was categorized based on a single fasting plasma glucose and HbA1c measurement. Previously undetected diabetes was defined as plasma glucose ≥7.0 mmol/L and/or HbA1c ≥6.5% (≥48 mmol/mol). Additionally, 3.9% had rheumatic disorders, and 2.1% had a history of cardiovascular disease, as per study protocol definitions. Regarding medication use, 18% of participants were on antihypertensive treatment, 7.2% were taking lipid-lowering medications, and 3.6% were using glucose-lowering medications, as reported during study enrollment. The proportion of current smokers was low (9.4%), while 31.3% were former smokers. The mean estimated glomerular filtration rate (eGFR) was 82.3 mL/min/1.73 m², the mean BMI was 26.9, and the mean waist circumference was 92.9 cm.

Associations between endostatin concentrations and other studied variables

The dataset used for SSVS was cleaned of missing values, resulting in a complete dataset of 4,576 individuals (9.0% missing data). The results of the SSVS analysis, with endostatin as the response variable, are presented in Table 2 and Figure 1. Hypertensive medication use was significantly associated with endostatin levels. Holding all other predictors constant (ceteris paribus), individuals on antihypertensive medication had an average endostatin increase of 0.08 standard deviations (SD) compared to those not on medication. Given the mean values of continuous predictors and a baseline value of zero for binary predictors, the expected endostatin level was 39,298 ng/L for individuals on hypertensive medication *vs* 38,545 ng/L for those without. Although this difference is relatively small compared to the range of quartile values (Table 1), the proportion of individuals on hypertensive medication increased from 12% in the first quartile to 26% in the fourth quartile. Waist circumference was positively associated with endostatin levels, increasing by 0.21 SD per 1 SD increase in waist circumference. However, this effect was mitigated by the influence of self-reported weight at age 20, where endostatin decreased by 0.11 SD per 1 SD increase in early adulthood weight. Kidney function, measured by eGFR, was inversely associated with endostatin levels. For each 1 SD increase in eGFR, endostatin decreased by 0.22 SD. Figure 2 illustrates this inverse relationship, showing the decline in average endostatin levels as a function of eGFR.

Inflammation, as measured by high-sensitivity C-reactive protein (hsCRP), was also associated with endostatin. Endostatin levels increased by 0.09 SD per 1 SD increase in hsCRP. Additionally, mean hsCRP levels rose from 1.3 mg/L in the lowest endostatin quartile to 2.6 mg/L in the highest quartile.

The Bayesian logistic regression analysis, which controlled for age, did not reveal any significant association between endostatin levels and overall coronary atherosclerosis in men, although nearly 50% of men exhibited signs of coronary atherosclerosis. However, severe coronary atherosclerosis (defined as >50% stenosis in the left main artery, proximal left anterior descending artery, or three-vessel disease) was significantly associated with higher endostatin levels, particularly at levels below the threshold of 45,813 ng/L (Figure 3).

For the Bayesian ZINB regression analysis, missing values were removed, resulting in a dataset of 4,870 individuals (3.1% missing data). The analysis, stratified by gender, did not reveal a sig-

nificant association between CACS and endostatin, after controlling for age.

Discussion

This cross-sectional study investigated the associations between endostatin levels and various cardiovascular and metabolic factors in a well-defined cohort of 5,026 randomly selected middle-aged individuals from the general population in Linköping, Sweden, as part of the Swedish CArdioPulmonary bioImage Study.

The key findings indicate that higher endostatin levels are significantly associated with increased waist circumference, elevated hsCRP (a marker of inflammation), antihypertensive treatment, decreased eGFR, and, in men, advanced coronary atherosclerosis.

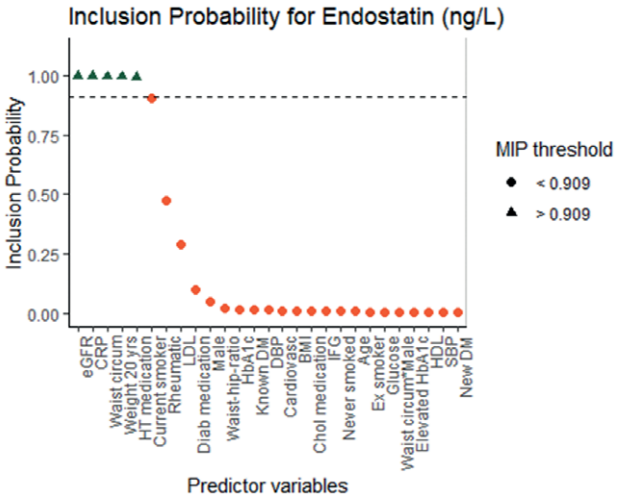

Figure 1. Posterior inclusion probabilities of the predictors from Table 2 (MIP), where a predictor is considered significant above the MIP threshold of 0.909 = 10/11.

Table 1. Baseline characteristics of the study. The data are presented as mean values ± SD or percentage values (in brackets).

	<32126	32126-37762	37762-44066	>44066	Total
Sample size	1256 (25)	1257 (25)	1257 (25)	1256 (25)	5026 (100)
Male	640 (51)	631 (50.2)	627 (49.9)	618 (49.2)	2516 (50.1)
<54 years	435 (34.6)	362 (28.8)	330 (26.3)	288 (22.9)	1415 (28.2)
54-56 years	230 (18.3)	264 (21)	246 (19.6)	234 (18.6)	974 (19.4)
57-60 years	300 (23.9)	323 (25.7)	312 (24.8)	338 (26.9)	1273 (25.3)
>=61 years	291 (23.2)	308 (24.5)	369 (29.4)	396 (31.5)	1364 (27.1)
Known DM	53 (4.2)	42 (3.3)	55 (4.4)	96 (7.6)	246 (4.9)
New DM	24 (1.9)	33 (2.6)	32 (2.5)	38 (3)	127 (2.5)
Elevated HbA1c	13 (1)	19 (1.5)	20 (1.6)	27 (2.1)	79 (1.6)
IFG	156 (12.4)	145 (11.5)	144 (11.5)	154 (12.3)	599 (11.9)
Normoglycemia	1010 (80.4)	1018 (81)	1006 (80)	941 (74.9)	3975 (79.1)
Rheumatic	39 (3.1)	42 (3.3)	47 (3.7)	67 (5.3)	195 (3.9)
Cardiovascular disease	25 (2)	19 (1.5)	26 (2.1)	37 (2.9)	107 (2.1)
HT medication	151 (12)	193 (15.4)	234 (18.6)	326 (26)	904 (18)
Chol medication	74 (5.9)	71 (5.6)	87 (6.9)	130 (10.4)	362 (7.2)
Diab medication	37 (2.9)	29 (2.3)	39 (3.1)	78 (6.2)	183 (3.6)
hsCRP, mg/L	1.3±2.7	1.8±3.7	1.9±3.4	2.6±4.8	1.9±3.8
LDL, mmol/L	3.2±0.9	3.3±0.9	3.3±1	3.3±1	3.3±1
HDL, mmol/L	1.7±0.5	1.7±0.5	1.6±0.5	1.6±0.5	1.6±0.5
Glucose, mmol/L	5.7±1.1	5.7±1.1	5.7±1.1	5.9±1.4	5.8±1.2
HbA1c, mmol/mol	35.6±6.2	35.9±6.2	36.1±6.7	37.2±8.3	36.2±6.9
Creatinine, umol/L	78.3±13.4	78.8±13.5	80.4±14.1	83.6±19	80.3±15.3
eGFR, mL/min/1.73m^2	84.7±11.4	83.9±11.1	81.8±12	78.9±13.1	82.3±12.1
SBP, mm Hg	130.3±16.7	132.4±17.3	133.1±18	134.5±17.6	132.6±17.5
DBP, mm Hg	81.8±9.8	83.1±10.1	83.6±10.6	84.8±10.5	83.3±10.3
Current smoker	106 (8.4)	113 (9)	118 (9.4)	133 (10.6)	470 (9.4)
Ex smoker	370 (29.5)	395 (31.4)	404 (32.1)	405 (32.2)	1574 (31.3)
Never smoked	728 (58)	700 (55.7)	690 (54.9)	673 (53.6)	2791 (55.5)
Body mass index, kg/m^2	26±4	26.6±4.2	27±4.3	28.1±4.9	26.9±4.4
Weight 20 yrs, kg	66±11.4	65.7±11.2	66.2±11.7	65.8±11.9	65.9±11.5
Waist circumference, cm	89.9±12.3	91.9±12.5	93.3±12.6	96.5±13.5	92.9±12.9
Waist-hip-ratio	0.9±0.1	0.9±0.1	0.9±0.1	0.9±0.1	0.9±0.1

Known DM, diabetes stated by study participant at medical history interview or in subject questionnaire; new DM, diabetes mellitus diagnosed at inclusion day 1 as fasting p-glucose ≥7.0 mmol/L or HbA1c ≥48 mmol/mol; elevated HbA1c = HbA1 c >42 mmol/mol and <48 mmol/mol; IFG, impaired fasting glucose defined as fasting p-glucose ≥6.1 mmol/L and < 7.0 mmol/L; rheumatic, self-reported rheumatoid arthritis, Bechterew's disease, psoriatic arthritis, SLE or Sjögren's syndrome; medications; HT, hypertension; Chol, on lipid lowering drugs; diab, on drugs for treatment of diabetes; SBP, systolic blood pressure; DBP, diastolic blood pressure; weight 20 years, self-reported weight at 20 years of age.

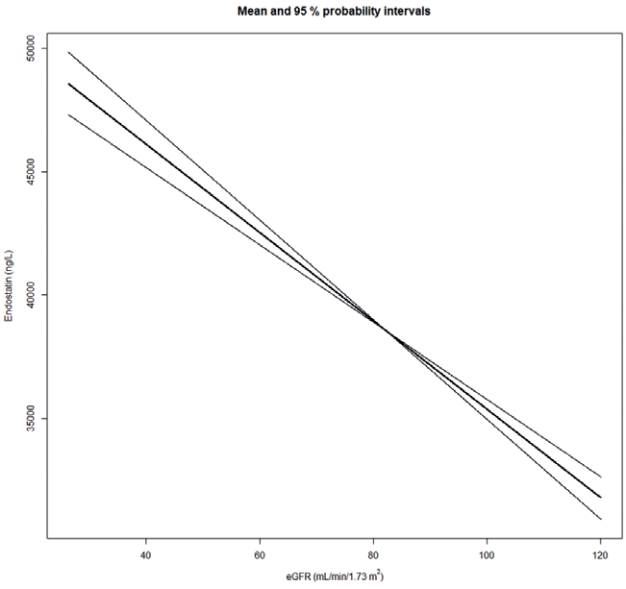

Figure 2. Given the average values of all continuous predictors and the value 0 for the 0/1 predictors, the expected values (middle line) and 95 % probability intervals (other, boundary, lines) of endostatin are shown as a function of eGFR.

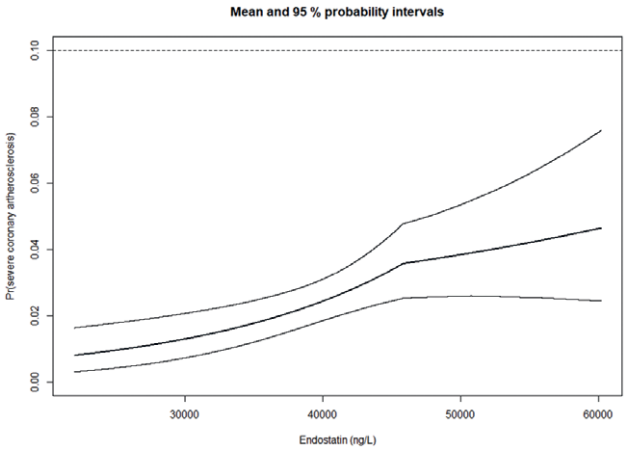

Figure 3. Probability of having severe coronary atherosclerosis, defined as more than 50% stenosis in left main artery (LM), proximal left descending artery or LAD or three vessel disease (3VD), for the average age of the men as a function of endostatin. The middle curve corresponds to the expected function and the other, boundary, curves correspond to 95 % probability intervals of the function.

Table 2. Results from SSVS with endostatin as response variable. The table shows the posterior inclusion probability for each predictor (MIP), the posterior mean of each regression coefficient (Avg Beta) and the 95 % credible (posterior probability) interval for each regression coefficient between "Lower CI" and "Upper CI".

Variable	MIP	Avg Beta	Lower CI (95%)	Upper CI (95%)
Male	0.0531	-0.0023	-0.0129	0.0000
Age, years	0.0093	0.0002	0.0000	0.0000
Known DM	0.0173	0.0002	0.0000	0.0000
New DM	0.0041	0.0000	0.0000	0.0000
Elevated HbA1c	0.0065	-0.0001	0.0000	0.0000
IFG	0.0109	-0.0002	0.0000	0.0000
Rheumatic	0.4728	0.0215	0.0000	0.0629
Cardiovasc	0.0122	0.0002	0.0000	0.0000
HT medication	0.9922	0.0775	0.0472	0.1080
Chol medication	0.0110	0.0002	0.0000	0.0000
Diab medication	0.0990	0.0039	0.0000	0.0386
hsCRP, mg/L	0.9958	0.0931	0.0648	0.1227
LDL, mmol/L	0.2898	0.0127	0.0000	0.0581
HDL, mmol/L	0.0058	0.0000	0.0000	0.0000
Glucose, mmol/L	0.0084	0.0001	0.0000	0.0000
HbA1c, mmol/mol	0.0177	0.0004	0.0000	0.0000
eGFR, mL/min/1.73m^2	0.9990	-0.2207	-0.2490	-0.1931
SBP, mm Hg	0.0055	0.0000	0.0000	0.0000
DBP, mm Hg	0.0169	0.0004	0.0000	0.0000
Current smoker	0.9054	0.0496	0.0000	0.0773
Ex smoker	0.0087	0.0001	0.0000	0.0000
Never smoked	0.0102	-0.0002	0.0000	0.0000
Body mass index, kg/m^2	0.0120	0.0004	0.0000	0.0000
Weight 20 yrs	0.9944	-0.1097	-0.1468	-0.0742
Waist circumference	0.9954	0.2139	0.1771	0.2530
Waist circumference*male	0.0074	0.0001	0.0000	0.0000
Waist-hip-ratio	0.0243	-0.0004	0.0000	0.0000

Known DM, diabetes stated by study participant at medical history interview or in subject questionnaire; new DM, diabetes mellitus diagnosed at inclusion day 1 as fasting p-glucose ≥7.0 mmol/L or HbA1c ≥48 mmol/mol; elevated HbA1c = HbA1 c >42 mmol/mol and <48 mmol/mol; IFG, impaired fasting glucose defined as fasting p-glucose ≥6.1 mmol/L and <7.0 mmol/L; rheumatic, self-reported rheumatoid arthritis, Bechterew's disease, psoriatic arthritis, SLE or Sjögren's syndrome; medications, HT: hypertension, Chol: on lipid lowering drugs, diab: on drugs for treatment of diabetes; SBP, systolic blood pressure; DBP, diastolic blood pressure; weight 20 years, self-reported weight at 20 years of age.

Summary of the literature

Despite extensive research, many fundamental aspects of endostatin remain unclear, including the precise origin of circulating endostatin and its physiological implications. Endostatin is primarily known as an angiogenesis inhibitor, suppressing endothelial cell proliferation, migration, and survival.

Increased endostatin concentrations are thought to reflect increased antiangiogenic activity, potentially leading to myocardial ischemia (due to decreased collateral formation)[22-24] and cerebral ischemia[25] but the literature reveals conflicting findings. Simultaneously, endostatin can impede neovascularization in atherosclerotic plaques, promoting plaque stabilization and suggesting a potential anti-angiogenic treatment for atherosclerosis.[26-28] However, the existing literature does not allow for a cohesive understanding of the pathophysiology, given the considerable variation in antiangiogenic responses at different endostatin concentrations, in various disease states, and in the presence of differences in the surrounding matrix.[29] Angiogenesis is crucial in obesity-related vascular remodeling.[30] The observed association between increased waist circumference and endostatin levels in this study aligns with experimental findings linking obesity to increased endostatin expression in animal models.[31] Similarly, previous research has demonstrated a link between endostatin and inflammation in chronic kidney disease, cardiovascular disease, and chronic obstructive pulmonary disease.[32,33]

Endostatin's role in atherosclerosis remains unclear, although elevated levels have been linked to extracellular matrix turnover and fibrosis. Experimental studies have shown that endostatin treatment reduces intimal neovascularization in mice[27] and rabbits[28] and slows atherosclerosis progression in animal models.[34,35] Additionally, increased circulating endostatin levels have been observed following myocardial infarction, likely due to elevated cardiac expression.[36] Endostatin has also been implicated in preeclampsia,[37] a hypertensive disorder, and has been linked to the duration and severity of hypertension, as well as target-organ damage in hypertensive individuals.[12] Previous studies have demonstrated that higher endostatin levels are associated with reduced eGFR and increased albuminuria, independently predicting chronic kidney disease (CKD) incidence in older adults.[10] Furthermore, elevated endostatin levels are associated with cardiovascular disease incidence and outcomes in CKD patients and the general population, suggesting broader systemic effects.[9]

Strengths and limitations

The findings of this study are consistent with previous research. To our knowledge, this is the first study examining endostatin levels in a middle-aged population cohort (50-64 years). Future large-scale prospective studies are needed to assess whether elevated endostatin levels predict cardiovascular events.

Several limitations should be noted. The study's cross-sectional design precludes causal inferences. Additionally, the study population was limited to individuals aged 50-64 from a single Swedish city, potentially limiting generalizability to other age groups or ethnic populations. Finally, the eGFR calculation methods used in this study may not be directly applicable to populations using different standard equations.

Conclusions

Higher endostatin levels in this middle-aged general population were significantly associated with antihypertensive medication use, increased waist circumference, reduced kidney function, and, in men, severe coronary atherosclerosis.

Contributions

AL, BW, TL, conceptualization, methodology, investigation, formal analysis, visualization, manuscript original drafting, reviewing and editing; TG, CJÖ, conceptualization, methodology, formal analysis, manuscript reviewing and editing; JA, conceptualization, methodology, investigation, formal analysis, manuscript reviewing and editing. All authors read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Conflict of interest

The authors declare no competing interests, and all authors confirm accuracy.

Ethics approval and consent to participate

All participants gave written, informed consent and the study was approved by the local Ethical Committee (DNo 2018/478) and by the National Ethics Review Authority (DNo 2021-00747).

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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