Keywords
Endostatin · Collagen XVIII · Angiogenesis · Renal diseases · Cardiovascular diseases

Abstract
Endostatin, a protein derived from the cleavage of collagen XVIII by the action of proteases, is an endogenous inhibitor known for its ability to inhibit proliferation and migration of endothelial cells, angiogenesis, and tumor growth. Angiogenesis is defined as the formation of new blood vessels from pre-existing vasculature, which is crucial in many physiological processes, such as embryogenesis, tissue regeneration, and neoplasia. Summary: Increasing evidence shows that dysregulation of angiogenesis is crucial for the pathogenesis of renal and cardiovascular diseases. Endostatin plays a pivotal role in the regulation of angiogenesis. Recent studies have provided evidence that circulating endostatin increases significantly in patients with kidney and heart failure and may also contribute to disease progression. Key Message: In the current review, we summarize the latest findings on preclinical and clinical studies analyzing the impact of endostatin on renal and cardiovascular diseases.

Introduction
In 1997, endostatin was first discovered in the conditioned media of a murine hemangioendothelioma cell line [1]. Endostatin is a 20-kDa C-terminal protein fragment cleaved from the NC1 domain of collagen XVIII by proteolytic reaction during the remodeling of extracellular matrix (ECM) [1, 2] (Fig. 1a). With the original discovery of endostatin, several publications have reported endostatin’s potential in inhibition of tumor growth, metastasis, and angiogenesis [1, 3, 4] (Fig. 1c). Notably, previous human studies imply that plasma endostatin levels are linked to multiple cancer types. Meanwhile, endostatin has been suggested as a biomarker with prognostic value in tumors, such as colorectal cancer, cervical...
Cleavage of endostatin involves many different proteases. Among them, the cathepsins, elastase, and matrix metalloproteinases (MMPs) play a key role [2, 8–10]. The 20-kDa endostatin fragment is generated via cathepsins [2, 8] or elastase [9], while MMPs are prone to produce larger fragments (Fig. 1b). Endostatin and its precursor collagen XVIII are identified as a common component expressed in nearly all epithelial and endothelial basement membranes (BM) [11–16], like those of blood vessels and renal tubules. Endostatin is known for its capability to inhibit angiogenesis and tumor growth by restricting the proliferation/migration of endothelial cells [1, 3] and by inducing apoptosis [17]. To date, there is no consensus about the molecular mechanisms of endostatin’s biological activity. Researchers have proposed several mechanisms implying complex and multiple pathways of endostatin regulation. It is widely accepted that endostatin regulates cell behavior by binding to a set of cell surface receptors, such as integrins, heparan sulfate proteoglycan (HSPG), vascular endothelial growth factor receptor (VEGFR) [18–20], and nucleolin [21, 22] (Fig. 1c).

A previous study proposed that the NC1 domain itself does not possess the ability to inhibit angiogenesis but endostatin does, after the activities of various proteinases [23], suggesting the important role of proteinases in endostatin activity. Cathepsin L was originally investigated in murine hemangioendothelioma cell cultures [8]. Subsequently, Ferreras et al. [2] further also confirmed that cathepsin L, B, and K can produce endostatin-like molecules with different efficiencies. Similarly, the formation of endostatin is also directly mediated by elastase [2, 9, 24]. Of note, cathepsin L and elastase are considered the most stable and efficient enzymes in the endostatin generation [8, 25]. MMPs, a family of zinc-dependent endopeptidases, can degrade nearly all ECM components and affect neovascularization. Alteration in the MMP levels influences local tumor progression and metastasis. Accumulating evidence also indicates that certain MMPs, especially cancer-related ones, play an essential role in generating biologically active endostatin. Recent studies have provided strong evidence that MMP-3, -7, -9, -13, -14, and -20 may participate in the generation of endostatin segments varying in molecular size, with the ability to regulate angiogenesis, endothelial cell proliferation, and migration in multiple diseases [2, 18]. However, it should be noted that these proteinases possess a dual function in regulating endostatin generation. Circulating endostatin levels may be systematically upregulated in kidney diseases (especially chronic kidney disease) [26–28] and cardiovascular diseases (CVDs) [29–31] and some neoplastic diseases [5–7] but mostly locally downregulated during tissue repair, wound healing, and chronic inflammation [24, 32], altogether implying complex regulatory pathways of endostatin generation (Fig. 1b).

Human endostatin shows biological activity by binding to multiple interacting receptors on the cell membrane, mainly containing integrins, HSPG, VEGFR, and nucleolin (Fig. 1c). However, the specific molecular mechanisms of endostatin activity are still incompletely understood. Initially, experimental data showed that endostatin binds to integrins α5β1 and αV (αVβ3/αVβ5) to counteract their bioactivity on endothelial cells, leading to inhibition of endothelial cell proliferation, migration, as well as angiogenesis and tumor growth [19, 20, 33, 34]. Subsequent studies indicate that endostatin can intensify its antiangiogenic action by binding to HSPG due to its special crystal structure with a heparin-binding region [35–37]. Furthermore, it has been reported that glypican, a subtype of HSPG on the cell surface, is an endogenous endostatin receptor [38, 39] that, despite low-affinity binding to endostatin, plays a key role in mediating endostatin activities [38]. Also, it is reported that endostatin blocks vascular endothelial growth factor (VEGF) actions by binding to various VEGFRs, such as VEGFR-1, -2, and -3 [40–43]. Kim et al. [41] showed that endostatin can directly bind to VEGFR-2, instead of VEGF, suggesting that this specific binding suppresses VEGF-induced endothelial cell migration, proliferation, and angiogenesis. Nucleolin is another endostatin receptor that may regulate its antiangiogenic and antitumor activity [21, 22].

Besides studies coming from the cancer field, recent studies showed that endostatin also plays an essential role in the pathogenesis of chronic kidney diseases (CKDs) and heart diseases. Increased levels of circulating endostatin are observed in the plasma/serum and in renal and myocardial tissue of animal models or patients with kidney or CVDs. However, whether endostatin action should be regarded as a protective or deleterious factor in these pathological processes remains controversial. In our preliminary study based on human kidney biopsy tissue (Fig. 2), we observed a distinct cytoplasmatic positivity for endostatin in epithelial cells of the Bowman capsule and tubular epithelium, as well as a weak expression in podocytes and endothelium of larger arteries and capillaries under physiological conditions. At the same time, capillaries, mesangium, interstitium, and media/adventitia of larger arteries in the renal cortex were typically neg-
Endostatin

Fibroblast

Epithelial cell

Basement membrane

Endothelial cell

Blood/blood cell

extracellular matrix

Trimerization domain

Hinge region

N-terminal domain

Interrupted triple-helical domain

Collagen type XVIII

NC1

a

MMPs

Endostatin-like protein fragments

Cathepsins, Elastases

20-kDa endostatin

Tissue repair

Wound healing

Chronic inflammation

Kidney diseases

Cardiovascular diseases

Some neoplastic diseases

N-terminal domain

NC1

b

Endostatin

(HSPG) Integrin VEGFR Nucleolin

Leading to renal microvascular rarefaction and fibrosis; potentialtional prognostic biomarker for occurrence and progression of kidney disease.

Inhibit progression of atherosclerosis and myocardial infarction

Induction of angiogenesis

Inhibition of endothelial cell proliferation and migration

Inhibition of tumor growth and invasion

Inhibition of cell apoptosis

(For legend see next page.)
ative, as shown in Figure 2a–c. Nevertheless, under pathological inflammatory conditions like interstitial nephritis, we could detect a strong expression of endostatin by plasma cells and loss of expression by tubular epithelial cells, likely due to inflammatory destruction, as shown in Figure 2d. In this review, we aimed to give an update of the previous studies about associations between endostatin and renal diseases and CVDs, involving preclinical and clinical studies. We hope this review can provide a concise summary of current knowledge of the physiological and pathophysiologic relevance of endostatin and thereby emphasize the significance of further research on decoding the endostatin pathways and their potential therapeutic use.

Fig. 2. Endostatin expression in renal cortex under physiological conditions (a–c) and in unspecific interstitial nephritis (d). a Glomerular capillaries (1) and mesangium (2) negative, podocytes (3) weakly positive, epithelial cells of the Bowman capsule strongly positive (4). b Tubular epithelium strongly positive (distal [5] > proximal [6]), interstitium (7) negative. c Endothelium of larger arteries (8) and capillaries (9) weakly positive, media/adventitia of larger arteries (10) negative. d In interstitial nephritis, plasma cells show strong positivity for endostatin (11). Inflammatory destruction of tubulin likely results in loss of endostatin expression. Immunohistochemistry on paraffin-embedded renal biopsy samples from patients from the University Medical Centre Mannheim, University of Heidelberg, Heidelberg, Germany (Primary antibody: Anti-Endostatin Polyclonal Antibody [bs-0547R]). Image acquisition was done using a PreciPoint scanning microscope (using objective ×40/0.65 NA) and MicroPoint software (v.2016-02-05; PreciPoint, Freising, Germany).

Fig. 1. Process of endostatin from generation to function. The figure depicts that collagen XVIII derived from epithelial and endothelial BM includes N-terminal domain, interrupted triple-helix domain and NC1 (a). NC1 is cleaved into 20-kDa endostatin and endostatin-like protein fragments by cathepsins, elastase, and MMPs. Based on previous animal and clinical studies, the levels of endostatin may be systematically upregulated in the kidney, cardiovascular, and some neoplastic diseases, in which circulating endostatin is regarded as a biomarker of occurrence/progression of the disease but mostly downregulated in tissue repair, wound healing, and chronic inflammation, in which locally decreased endostatin may be beneficial for organ/tissue recovery (b). Endostatin binds to integrins, HSPG, VEGFR, and nucleolin to exert different functions on the cell surface, including inhibition of ECs proliferation and migration and induction of apoptosis, which are related to inhibition of angiogenesis. Also, it was reported that endostatin may lead to renal fibrosis in murine models and be a potential prognostic biomarker for the occurrence and progression of kidney diseases. Moreover, in CVD, endostatin may inhibit the progression of AS and MI (c). BM, basement membrane; NC1, C-terminal domain; MMPs, matrix metalloproteinases; HSPG, heparan sulfate proteoglycans; VEGFR, vascular endothelial growth factor receptor; ECs, endothelial cells; CVD, cardiovascular disease; AS, atherosclerosis; MI, myocardial infarction.
Endostatin in Preclinical Studies

Endostatin is well-known as a potent inhibitor of angiogenesis, with the ability to regulate endothelial cell proliferation and migration in vivo and in vitro. Recently, some animal studies have provided evidence that serum concentration and expression of endostatin in the kidney and heart tissues increase significantly in kidney and CVDs.

Animal Models of Renal Diseases

Recently, increasing evidence indicates that endostatin is highly expressed in the kidney tissue and serum in various experimental kidney disease models, probably being an early predictive factor for disease progression. Endostatin antiangiogenic activity may be a beneficial novel therapeutic target. Additionally, the association between increased serum endostatin and renal fibrosis in aging mice may provide a mechanistic link of fibrogenesis in CKD.

In previous studies, researchers showed endostatin mRNA and protein expressions were upregulated during ischemia in murine models of the unilateral ureteral obstruction and ischemia/reperfusion-induced acute renal failure (ARF), thus suggesting endostatin may take part in the process of pathophysiology and fibrosis of renal injury [44, 45] (Table 1). Concordant results could be as well observed in a mouse model with experimental endotoxemic ARF. In this study, Hamano et al. [46] showed that collagen XVIII/endostatin deficiency aggravates immune-mediated glomerulonephritis, potentially via remodeling matrix and promoting capillary rarefaction, the inflammatory response, and vascular endothelial cell damage. Additionally, it is showed that endostatin staining increased in the BM in mice with ARF [47]. Measurement of serum endostatin concentration has been proven to be an earlier and more sensitive predictive indicator for the progression of renal disease than blood urea nitrogen, a typical indicator for assessment of kidney function, in mice with the glomerulonephritis phenotype [48]. Antiangiogenic therapy can significantly improve renal interstitial fibrosis [49] and reduce urinary albumin excretion in mice models of early experimental diabetes or diabetic nephropathy [49, 50], suggesting that endostatin may play a key role in the antiangiogenic treatment of early diabetic nephropathy.

Based on animal studies, it was suggested that the progression of CKD might be – among other factors – caused by rarefaction of renal microvascular, hence leading to subsequent renal fibrosis [51–54]. Furthermore, experimental studies indicated that endostatin expression is a powerful marker of renal microvascular rarefaction [55, 56]. In animal models of CKD, Lin et al. [57] demonstrated that the circulating levels of endostatin are significantly increased in blood and tissue in aging mice compared to young animals, especially in the renal tissue. In these experimental models, a positive correlation between increased endostatin levels and microvascular rarefaction with consecutive progressive renal fibrosis in aging mice could be observed. In 2016, Lin et al. [58] repeatedly confirmed overexpressed endostatin to be present in an aging mouse kidney presumably provoking alone renal interstitial fibrosis. Besides, they also observed that renal fibrosis even developed in young mice transgenic to overexpress

| First author  | Species | Renal disease model | Main findings |
|---------------|---------|---------------------|---------------|
| Bellini et al. [44] | Mice | ARF | Increased glomerular and tubular expression of endostatin after ischemia and reperfusion |
| Maciel et al. [45] | Mice | UUO | Endostatin expression increased in injured tissue, especially on tubular cells, in UUO |
| Hamano et al. [46] | Mice | ARF | Endostatin expression increased in the glomerular BM and Bowman’s capsule in wild-type mice with ARF |
| Gicy et al. [47] | Mice | ARF | Endostatin staining increased in the BM in ARF mice |
| Wallwitz et al. [48] | Mice | Glomerulonephritis | Serum endostatin concentration was increased earlier than BUN in the early stage of glomerulonephritis |
| Bai et al. [49] | Rat | Experimental diabetes | Endostatin treatment improved interstitial fibrosis and reduced urine albumin excretion |
| Tanabe et al. [50] | Mouse | Diabetic nephropathy | Endostatin inhibits albuminuria and glomerular alterations |
| Lin et al. [57] | Mice | – | Serum endostatin levels significantly increased about 5–6 fold in aging mice |
| Lin et al. [58] | Mice; transgenic mice | – | Endostatin overexpression causes renal interstitial fibrosis |

UUO, unilateral ureteral obstruction; ARF, acute renal failure; BUN, blood urea nitrogen.
endostatin or treated with 28-day endostatin delivery via osmotic minipumps implanted subcutaneously. An increased proportion of senescent cells in young mice with endostatin exposition was also observed in this study.

**Animal Models of CVDs**

Previous preclinical studies were predominantly focused on animal models of several CVDs, including myocardial infarction (MI), atherosclerosis (AS), and cardiac hypertrophy (CH), as shown in Table 2. In established MI models, previous studies reported endostatin expression was upregulated in the heart tissue [55, 59], and serum endostatin concentration increased remarkably [59]. Isobe et al. [59] also showed anti-endostatin antibody therapy increased left ventricular (LV) remodeling and heart failure (HF). Furthermore, inhibition of endostatin aggravates the outcomes after MI in rats. Subsequently, the review by Maemura [60] provided convincing evidence that endogenous endostatin participates in the pathophysiologic processes of LV remodeling and HF in MI mice and that the antiangiogenic activity of endostatin might prove a protective agent in the cardiovascular system by decreasing intimal neovascularization and plaque growth in apoE −/− mice. In 2018, in concordance with the previous studies, Sugiyama et al. [61] observed increased endostatin expression in rat models of MI but also impaired cardiac function in CO-L18A1-deficient rats, suggesting that endostatin may play an important role in post-infarct myocardial healing by activating proliferation and migration of myofibroblasts. In 1999, the group of Moulton et al. [62] was the first to describe the association between endostatin expression and plaque growth in apoE −/− mice. Moreover, it has been shown that all antiangiogenic inhibitors including endostatin could reduce plaque growth and intimal neovascularization after long-term treatment [62]. In animal models of AS, previous studies by Moulton et al. [63] and Zeng et al. [64] demonstrated that loss of collagen XVIII/endostatin enhances plaque neovascularization and vascular permeability. Subsequently, some endostatin-related products, such as recombinant endostatin, endostatin gene treatment, and Endostar, N-terminal modified endostatin, also showed the ability to inhibit neovascularization and development of AS [65–67].

| First author          | Species | CVDs models    | Main findings                                                                 |
|-----------------------|---------|----------------|-----------------------------------------------------------------------------|
| Qipshidze et al. [55] | Mice    | MI             | Cardiac endostatin expression increased after MI                            |
| Isobe et al. [59]     | Rat     | MI             | Expression of endostatin in cardiomyocytes and serum endostatin levels were increased in the MI rat model; endostatin neutralization worsened LV remodeling and HF |
| Maemura [60]          | Mice    | MI             | Endostatin participates in the pathophysiologic process of LV remodeling and HF in MI mice |
| Sugiyama et al. [61]  | Rat     | MI             | Proliferation and migration of myofibroblasts were increased by endostatin in vitro |
| Moultonet al. [62]    | Mice    | AS             | Endostatin reduces plaque growth and intimal neovascularization in apoE −/− mice |
| Moulton et al. [63]   | Mice    | AS             | Vasa vasorum and intimal neovascularization were more extensive; enhanced vascular permeability in collagen XVIII-knockout mice bred into the AS-prone apoE −/− strain |
| Zeng et al. [64]      | Mice    | AS             | Increased neovascularization and vascular permeability in AS-prone mice with loss of collagen XVIII gene expression |
| Zhu et al. [65]       | Mice    | AS             | Endostatin gene transfer to the muscles of apoE −/− mice significantly improves the stenosis rate of the aorta |
| Mao et al. [66]       | Rabbit  | AS             | The intima-media thickness ratio and the number of neovessels was distinctly less in the recombinant endostatin treated group |
| Xu et al. [67]        | Swine   | AS             | Endostar treatment significantly reduced IMT and vasa vasorum density |
| Dai et al. [68]       | Rat     | CH             | Endostatin overexpression decreased heart weight and cardiomyocyte size, ANP, and BNP in a rat model of CH |
| Yasuda et al. [69]    | Guinea pig | CH          | Endostatin inhibited T-type Ca (2+) current, namely low voltage-activated Ca (2+) current channel which is related to the development of CH |
| Imoto et al. [70]     | Rat     | CH             | Endostatin inhibited T-type Ca (2+) channel activity |
| Givvimani et al. [71] | Mice    | Compensated and decompensated CH | Endostatin is involved in the transition from compensated left ventricular hypertrophy to decompensatory HF |
| Nikolova et al. [72]  | Rabbit  | Compensated and decompensated CH | MMP-9 increased endostatin; endostatin is inversely correlated to capillary density |

MI, myocardial infarction; AS, atherosclerosis; LV, left ventricular; apoE −/−, apolipoprotein E-deficient; IMT, intima-media thickness; CH, cardiac hypertrophy; ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide; MMP, matrix metalloproteinase; CVDs, cardiovascular diseases; HF, heart failure.
Concerning studies in animal models of CH, Dai et al. [68] indicated that overexpression of endostatin could mitigate CH by the cAMP-PKA signaling pathway in rats. However, Yasuda et al. [69] and Imoto et al. [70] showed that endostatin inhibits the progress of CH mainly through inhibiting T-type Ca (2+) channel expression. In established hypertrophy, a report conducted by Givviman et al. [71] described that expression of endostatin was increased in decapensated hearts, while not in compensated hearts. Nikolova et al. [72] demonstrated that downregulation of endostatin could preserve capillary density and prevent the development of HF in animal models of LV pressure overload hypertrophy.

Thus, in general, endostatin expression increases in animal models of CVDs and loss of endostatin in mice models aggravates the disease outcome. Endostatin’s ability to inhibit neovascularization in AS may be a novel therapeutic approach.

**Endostatin in Clinical Studies**

CKD has become one of the most important problems affecting global human health. CKD has been increasing in prevalence and is associated with high mortality. CVD is one of the major complications of CKD. However, the specific mechanisms explaining the association between CKD and CVD are incompletely understood. Recently, microvascular disease has been reported as one of the major contributors to the pathogenesis of CKD and CVD [73]. Moreover, angiogenesis is an important component in the physiological and pathological processes of renal and CVDs. Additionally, a link between serum endostatin levels and pathogenesis of CKD and CVD in clinical studies has been suggested.

**Endostatin in Kidney Disease**

The estimated glomerular filtration rate and albuminuria are classical CKD progression biomarkers and thus used for disease classification [48]. Beside these classical well-established clinical risk factors, it became obvious that hormones/factors involved in blood vessel formation and growth regulation may also be involved in CKD progression.

In the past decade, the influence of circulating endostatin on CKD has been mostly explored in animal models. Only recently, a limited number of clinical studies addressed this question. Increased serum levels of endostatin have been observed in 60 CKD patients with moderately impaired renal function compared to 15 normal controls [74] (Table 3). Subsequently, the findings were confirmed in a study with 139 CKD patients [75]. Accordingly, in 2012, Chen et al. [26] reported that plasma endostatin levels were much higher in patients with CKD than in those without CKD. In contrast to the pilot study conducted by Futrakul et al. [74], Chen et al. [26] studied more patients and provided information on GFR and albuminuria. Meanwhile, a review by Tanabe et al. [27] showed that the antiangiogenic factor endostatin may be involved in the pathogenesis of CKD, also a biomarker of progression of CKD. Ruge et al. [28] studied elderly patients, collecting clinical data from 2 independent longitudinal communities. Their findings in the elderly patients identified circulating endostatin as an independent predictor of incident CKD that increased with a decline in GFR and an increase in albuminuria. Another report observed remarkably high mean plasma levels of endostatin in hemodialysis patients, regardless of the type of heparin used [76].

In patients with type 2 diabetes, Carlsson et al. [77] described circulating endostatin as a promising predictor for the prediction of progression of kidney disease and mortality. Their findings showed that circulating endostatin levels in participants with diabetic nephropathy were higher than those without nephropathy at baseline ($p = 0.031$). The study by Chauhan et al. [78] also showed similar findings. Moreover, our present study showed that serum endostatin concentration at baseline is an independent prognostic factor of graft loss in kidney transplant recipients, demonstrating higher sensitivity than classical risk factors, such as GFR and albuminuria [79]. Also, dynamic plasma endostatin combined with other clinical data improves the predictive power of 30-day mortality in AKI [80]. Moreover, endostatin positively correlated with the severity of AKI in critically ill patients but had limited predictive value regarding AKI, need for renal replacement therapy (RRT), and 90-day mortality [81].

The aforementioned clinical studies imply that circulating endostatin levels may be a potential prognostic biomarker for the occurrence and progression of CKD, as well as mortality. In addition to CKD-relevant disease, one clinical study showed that plasma endostatin levels were independently related to incident cardiovascular events in CKD patients during the 46-month follow-up period [82]. Overall, these data suggest that endostatin might be a potential therapeutic target in the treatment of both CKD and CVD.
The Role of Endostatin in Renal and Cardiovascular Diseases

CVDs are the leading cause of death and chronic disability worldwide [83]. Over the past decades, traditional clinical diagnostic and prognostic parameters of CVDs have included among others, such as age, sex, low-density lipoprotein cholesterol, smoking, blood pressure, blood glucose, NT-proBNP, and troponins [84]. Recently, accumulating evidence has shown that endostatin plays an important role in the progression of AS and serves as a promising biomarker for subsequent CVD [85].

Circulating endostatin levels are increased in CVD animal models, as mentioned earlier. The same findings have also been repeatedly reported in patients with CVD. It is believed that increased endostatin levels increase the incidence of myocardial ischemia (MI), due to its antiangiogenic properties. Previously, a series of clinical studies demonstrated the association of elevated endostatin with the reduced collateral formation in various CVDs [86–90] (Table 4). Increased circulating endostatin has also been linked to poor outcomes in chronic HF (CHF) and pulmonary arterial hypertension [91, 92]. Patients with ≥5-year hypertension history had higher serum endostatin levels than normotensive patients. Moreover, raised serum endostatin has been related to a longer duration of hypertension and a higher incidence of hypertension-related target-organ damage, such as vascular, myocardial, and renal damage [30]. Notably, the predictive role of endostatin is contradictory in CHF patients. Some

| Table 3. Clinical studies of endostatin in patients with kidney diseases |
|--------------------------------------------------|
| First author                               | Number of patients/controls                                                                 |
| Futrakul et al. [74]            | 75 participants in total, 60 CKD patients with moderately impaired renal function, and 15 normal controls |
| Wątorek et al. [75] | 139 CKD patients in total, 67 patients without dialysis versus 46 HD patients versus 26 patients on peritoneal dialysis (PD) |
| Chen et al. [26] | 402 participants in total, 201 CKD patients, and 201 controls |
| Ruge et al. [28] | 1,601 elderly from 2 independent longitudinal community-based cohorts (786/815) |
| Rydzewska-Rosolowska et al. [76] | 17 chronic HD patients |
| Carlsson et al. [77] | 607 patients with T2D |
| Chauhanet al. [78] | 1,245 patients in total, 374 patients in ACCORD trial (187 matched case-control pairs), and 871 T2D patients with preserved eGFR from ISMMS BioMe Biobank |
| Chu et al. [79] | 574 maintenance KTRs in total; 37 graft loss versus 537 nongraft loss |
| Jia et al. [80] | 256 new-onset AKI patients |
| Mårtensson et al. [81] | 1,112 patients in ICUs, 20% early AKI vs.18% developed late AKI versus 62% non-AKI |
| Kanbay et al. [82] | 519 CKD pre-dialysis patients |

Endostatin in CVDs

CKD, chronic kidney disease; HD, hemodialysis; PD, peritoneal dialysis; RRT, renal replacement therapy; eGFR, estimated glomerular filtration rate; ACR, urinary albumin-to-creatinine ratio; T2D, type 2 diabetes; ACCORD, the Action to Control Cardiovascular Disease; ISMMS, the Icahn School of Medicine at Mount Sinai; KTRs, kidney transplant recipients, AKI, acute kidney injury; ICUs, intensive care units; CVEs, cardiovascular events.
endostatin is not directly associated with indices of HF [93, 94], while other data support the prognostic value of circulating endostatin for the severity of diastolic dysfunction in HF patients with preserved ejection fraction [29] and higher HF risk in healthy elderly individuals [31]. Additionally, endostatin could predict all-cause mortality in patients with CHF [93, 95]. Although recombinant human endostatin combined with chemoradiotherapy has been shown to significantly improve survival in some cancer patients, its cardiotoxicity, such as endostatin-associated acute HF, has to be noted [96, 97].
Taken together, endostatin seems to be a robust and promising prognostic biomarker for the progression and mortality of CVD. Animal and clinical studies indicated that endostatin may play different roles in different stages of CV diseases (Fig. 3). However, specific mechanisms explaining the association between endostatin and CVDs remain unclear.

**Potential Pharmacologic Intervention in the Endostatin System**

Angiogenesis, defined as a formation of new blood vessels from pre-existing vasculature, is fundamental to many pathophysiologic processes, including nonneoplastic diseases such as embryogenesis, tissue regeneration, and neoplastic diseases [98]. In 1971, Folkman [4] first suggested that the growth of solid tumors relies on angiogenesis to meet the requirements of oxygen and nutrient supply for tumor cells to survive [1]. Subsequently, with the discovery of endostatin, endostatin has been studied intensively about tumor treatment. Endostar, derived from recombinant human endostatin, has been originally approved to treat non-small-cell lung cancer by China's State Food and Drug Administration in 2005. Consecutively, endostatin has been widely used in antiangiogenesis therapy of human various cancer treatments, including melanoma tumor, hepatoma, breast cancer, and colon/rectal cancer [99–103].

In addition to the possible use of endostatin for cancer treatment, animal studies also indicate possible antifibrotic properties of endostatin. Animal studies have shown that endostatin can favorably affect fibrosis of both internal organs and skin [104, 105]. In a rat MI model, anti-endostatin antibody therapy exacerbated the extent of fibrosis [59]. However, the specific molecular

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**Fig. 3.** Stage-dependent role of endostatin in CVDs. The figure illustrates the potential role of endostatin in various stages of CVDs, including early plaque formation and growth, early and late stage after MI as well as established HF. CVDs, cardiovascular diseases; MI, myocardial infarction; LV, left ventricular; HF, heart failure.
mechanisms regarding the inhibitory effect of endostatin on fibrosis are not fully understood. Transforming growth factor-β plays a central role in fibrotic organ remodeling [104]. Endostatin has been shown to reduce transforming growth factor-β and α-SMA expression in a mouse model of peritoneal sclerosis [106] and in an animal model of liver fibrosis [107]. Furthermore, in an animal model of pulmonary fibrosis, Wan et al. [108] showed that endostatin can attenuate fibrosis through inhibition of the VEGF/VEGFR pathway and activation of extracellular signal-regulated protein kinase 1/2. VEGF is an important pro-angiogenic regulator involved in pathological scar formation [109, 110]. In a study by Wang et al. [108], Endostar was shown to reduce hypertrophic scar formation by downregulating the expression of VEGF and TIMP-1, an endogenous inhibitor of MMPs, in a rat model [105]. Platelet-derived growth factor receptor (PDGFR) signaling pathway is involved in fibrosis formation and has emerged as a new target for the treatment of fibrosis. Li et al. [111] reported that endostatin inhibits fibrosis in human skin fibroblasts by regulating protein expression of p-PDGFRβ, PDGFRβ, and p-ERK.

To date, pharmacologic strategies of endostatin for either renal or CVDs are still at a very early stage. We may get some first helpful insights from studies designed primarily for treating cancer, since this field is more advanced.

Conclusions

Endostatin is a 20-kDa C-terminal protein fragment cleaved from the NC1 domain of collagen XVIII by proteolytic reactions during the remodeling of the ECM. Endostatin and its precursor collagen XVIII are identified as a common component expressed in nearly all epithelial and endothelial BMs, for example, in blood vessels and renal tubules. Endostatin is known for its capability to inhibit angiogenesis and tumor growth by restricting the proliferation/migration of endothelial cells and by inducing apoptosis. Impairment of angiogenesis is a hallmark of chronic heart and kidney failure, and endostatin is involved in these processes in CKD and HF. Since endostatin is not just a biomarker of angiogenesis but also a hormone regulating these processes, pharmacologic intervention in this system might offer new therapeutic options in the future.

Acknowledgements

We thank Dr. G. Berg from Biomedica Medizinprodukte GmbH, Vienna, Austria, for providing antibodies against human endostatin.

Statement of Ethics

An ethics statement is not applicable because this study is based exclusively on published literature.

Conflict of Interest Statement

The authors declare no conflict of interest.

Funding Sources

The authors have no funding sources to report.

Author Contributions

Mei Li, Chang Chu, and Berthold Hocher wrote the manuscript. Bernhard K. Krämer and Zoran Popovic revised the manuscript.

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