Antiangiogenic therapy in diabetic nephropathy: A double-edged sword (Review)

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Received August 20, 2020; Accepted January 21, 2021

DOI: 10.3892/mmr.2021.11899

Abstract. Diabetes and the associated complications are becoming a serious global threat and an increasing burden to human health and the healthcare systems. Diabetic nephropathy (DN) is the primary cause of end-stage kidney disease. Abnormal angiogenesis is well established to be implicated in the morphology and pathophysiology of DN. Factors that promote or inhibit angiogenesis serve an important role in DN. In the present review, the current issues associated with the vascular disease in DN are highlighted, and the challenges in the development of treatments are discussed.

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Abbreviations: ACEI, renin angiotensin enzyme inhibitors; Angs, angiopoietins; bFGF, basic fibroblast growth factor; CKD, chronic kidney disease; DN, diabetic nephropathy; ESRD, end-stage renal disease; GFR, glomerular filtration rate; GBM, glomerular basement membrane; HIF-1, hypoxia inducible factor-1; IGF-1, insulin-like growth factor-1; KBP, kallikrein-binding protein; OIR, oxygen-induced retinopathy; PDGF, platelet-derived growth factor; RAAS, renin-angiotensin-aldosterone system; RSV, resveratrol; PAR2, protease-activated receptor 2; sFLT-1, soluble FMS-like tyrosine kinase-1; TSP-1, thrombospondin-1; VASH1, vasohibin-1; VEGF, vascular endothelial growth factor

Key words: DN, ESRD, abnormal angiogenesis, promote angiogenesis, inhibits angiogenesis, antiangiogenic therapy

Contents

1. Introduction

Diabetic nephropathy (DN) is clinically defined as microalbuminuria with or without other microvascular lesions or angiopathies, followed by a gradual increase in the extent of proteinuria and a decrease in the glomerular filtration rate, in a patient with long-term diabetes (1). DN is the primary cause of chronic kidney disease (CKD) that results in progressive renal hypofunction, with ~50% of patients progressing to end-stage renal disease (ESRD) in the USA (2,3). Studies on DN indicate that 20-30% patients with type I and II diabetes will progress to CKD and may eventually progress to ESRD (4,5).

The structural damage to the glomerular filtration barrier, as well as proteinuria are the primary features of DN, in addition to ultra-structural alterations, glomerular basement membrane thickening, mesangial matrix expansion, nodular glomerulosclerosis, arteriolar hyalinosis, podocyte foot process fusion and detachment (6). The occurrence of these injuries is due to the imbalance between the destructive factors (such as advanced glycation end products, free radicals, immune agents, andpro-inflammatory and pro-fibrotic molecules) and protective factors (such as anti-inflammatory agents, anti-ROS molecules and anti-fibrotic molecules) in the kidney (7-11).

Although glomerular mesangial cells and podocytes are considered to be the primary mediators of DN, the microvascular system damage caused by diabetes also serves a key role in the pathogenesis. Similar to diabetic retinopathy, biopsy in patients with type 1 diabetes showed increased glomerular capillary density and an increased number of glomerular efferent arterioles caused by glomerular neovascularization (12,13). In addition, the glomerular expression of vascular growth factors, including angiogenin and vascular endothelial growth factor (VEGF) increases (12,14,15), which

may cause DN by promoting vascular leakage and decreasing transendothelial electrical resistance (14,16).

At present, the treatment of DN is primarily aimed at controlling blood glucose levels and lowering blood pressure using specific types of blood pressure drugs that block the renin-angiotensin-aldosterone system (RAAS). RAAS inhibitors have been shown to exhibit renal protection in patients with DN, but it is not always certain whether their efficacy is sufficient. Similarly, in large clinical trials, strict blood glucose control has led to inconsistent benefits for patients with kidney disease. Therefore, once obvious DN occurs, in addition to the use of RAAS inhibitors to control blood pressure and blood glucose, specific therapies for the underlying mechanisms are also required to prevent DN developing into ESRD.

In several animal experiments, angiogenesis has been shown to be a potential target for the early treatment of DN. VEGF is the primary mediator of abnormal diabetic glomerular angiogenesis. Although the beneficial effects of anti-VEGF antibodies have been confirmed in diabetic animal experiments, recent basic and clinical evidence has suggested that blocking VEGF signaling can lead to proteinuria and renal thrombotic microangiopathy (17), indicating the importance of the normal levels of VEGF in the kidney. Therefore, anti-angiogenic treatment of DN should eliminate the excessive angiogenic response of the glomeruli without accelerating endothelial damage. Some endogenous anti-angiogenic factors, such as tumorstatin and endostatin, inhibit the excessive activation of endothelial cells, but do not specifically block the signal transduction of VEGF. In addition, the novel endothelial-derived anti-angiogenic factor vasohibin-1 (VASH1) improves stress tolerance and the survival of endothelial cells, and inhibits excessive angiogenesis. These anti-angiogenic factors have been shown to inhibit proteinuria and glomerular changes in diabetic mouse models (18). Therefore, anti-angiogenic treatments with promising drug candidates may improve the renal prognosis of patients with early DN.

In the present review, the formation and possible causes of abnormal angiogenesis in DN are summarized, and integrated related treatment options are discussed, with the aim of highlighting potential novel avenues for future research and clinical treatment.

2. Abnormal angiogenesis in DN

Angiogenesis refers to the physiological and pathological process of neovascularization based on already present vessels. It is associated with embryogenesis, wound healing, tumor growth and metastasis, atherosclerosis and human inflammatory diseases (19). Abnormal angiogenesis is always associated with the morphology and pathophysiology of DN. Initially, it was reported that the formation of new blood vessels in the glomeruli of patients with type I and II diabetes represented abnormal angiogenesis (12,20,21), and abnormal blood vessels were discovered in the glomerular tuft area, the glomerular vascular pole and Bowman's capsule (21,22). A large number of proangiogenic and anti-angiogenic factors are involved in the regulation of angiogenesis, including VEGF, angiopoietins, fibroblast growth factors (FGFs), transforming growth factor-1 β (TGF-1β) and ephrin, amongst others.

Proangiogenic factors

VEGFs. As is presented in Table I, VEGF or VEGF-A is a critical inducer of angiogenesis, and its expression in the glomerulus is involved in the pathogenesis of DN. It has been suggested that the oxygen-regulated protein 150 kDa (ORP150) may be involved in the development of proteinuria by regulating VEGF secretion in DN, as ORP150 expression is upregulated in patients with DN (23). Blockade of VEGF signaling with the pan-VEGF receptor tyrosine kinase inhibitor, SU5416, ameliorated diabetic (type II) albuminuria in a mouse model (24). Administration of neutralizing anti-VEGF antibodies in type I and II diabetic animals decreased proteinuria and glomerular hypertrophy (16,25,26). Treatment with resveratrol, a polyphenol with anti-angiogenic activity, decreased the increase in glomerular diameter, mesangium accumulation, glomerular basement membrane thickness and renal fibrosis in a DN rat model, by decreasing the expression of pro-angiogenic factors, such as VEGF (27). Chemerin is a fat cell factor that participates in regulating inflammation. A previous study reported that the expression of chemerin and VEGF was associated with inflammatory factors and renal function in a DN rat model (28). Intravitreal injections of VEGF inhibitors can lead to a chronic decline in renal function (29). Additionally, the activation of protease-activated receptor 2 (PAR2) can generally exacerbate diabetic kidney disease, but PAR2 can protect against VEGF inhibitor-induced kidney damage (30).

The *VEGF-A* gene produces five closely associated subtypes via alternative splicing, and the most abundantly expressed species is *VEGF-A*$_{165}$, which encodes a glycoprotein with 20% homology to the A and B chains of platelet-derived growth factor (PDGF) (31). Renal *VEGF-A* gene expression is increased at the early stages and remains high at the later stages of diabetes in rats (32). There have been controversial results regarding the expression of *VEGF-A* in glomeruli of DN. Immunohistochemical analysis of renal biopsy showed that VEGF-A expression in the glomeruli was increased in the early stages of DN (33). However, the expression of *VEGF-A* mRNA in the glomeruli of patients with DN was decreased by oligonucleotide microarray analysis (34). The increase of VEGF-A expression in the serum of patients with type II diabetes is associated with blood glucose control, high levels of the sensitive C-reactive protein and proteinuria, suggesting that *VEGF-A* is a biomarker of diabetic inflammation and nephropathy (35). Serum *VEGF-A* levels are significantly correlated with hypoxia inducible factor-1 (HIF-1) and insulin-like growth factor-1 (IGF-1), which is hypothesized to be associated with the pathogenesis of DN (36). Podocyte specific *VEGF-A* heterozygous deficient mice showed proteinuria and glomerular endothelial damage similar to preeclampsia, whereas podocyte-specific *VEGF-A*$_{165}$ overexpressing mice showed significant striking collapsing glomerulopathy (37). *VEGF-A* decreases the levels of inhibitory complement factor H in the kidney, and this known genetic alteration is a feature of hereditary thrombotic microangiopathy, suggesting that *VEGF-A* is involved in the local regulation of the complement system (38). Under the control of α-1 antitrypsin promoter, transgenic rabbits expressing *VEGF-A*$_{165}$ in the kidney and liver also showed progressive proteinuria and renal dysfunction, early glomerular capillary hyperplasia and podocyte hypertrophy, late glomerular sclerosis and glomerular villus collapse (39).

Eremina *et al* (40) found that when the *VEGF-A* gene was conditionally deleted from the podocytes of adult mice, an increase in proteinuria, thrombus and capillary ring occlusion in capillaries and endothelial cell swelling were observed, which is similar to renal thrombotic microangiopathy (40). On the other hand, overexpression of *VEGF-A* in podocytes of adult transgenic mice leads to proteinuria, glomerular enlargement, glomerular basement membrane thickening, mesangial expansion and podocyte disappearance (41). In addition, overexpression of mutant *VEGF-A*, which selectively stimulates VEGFR-2, leads to mesangial matrix expansion and endothelial cell proliferation (42). In a case-controlled study, it was shown that serum VEGF-A was more preferable than that in plasma as a marker reflecting diabetic control in patients with type II diabetes, since a large portion of VEGF-A is derived from platelets (35). Kidney injury was partially prevented using DIAVIT, a natural *Vaccinium myrtillus* (blueberry) and *Hippophae Rhamnoides* (sea buckthorn) extract, due to the alteration of VEGF-A splicing in type II DN, particularly with delphinidin (43).

VEGF is a heparin-binding growth factor specific for vascular endothelial cells to promote angiogenesis *in vivo* (44). VEGF-A increases vascular permeability and monocyte chemotaxis (45,46). VEGF-A binds to tyrosine kinase receptor VEGFR-1 (Flt-1) and VEGFR-2 (KDR/Flk-1), activating them (47). The angiogenic signal primarily comes from VEGF-A binding to VEGFR-2, whereas VEGFR-1 can be used as a negative regulator of VEGF-A, at least under certain conditions, such as embryogenesis (1). In addition, the activation of VEGFR-2 inhibits the apoptosis of endothelial cells via a PI3K Akt pathway (48). The synergistic effect of hyperglycemia and increased VEGF-A levels in diabetic glomerulopathy can be explained by the unique hypothesis of 'VEGF-endothelial nitric oxide (NO) uncoupling' (49,50).

VEGF-B is expressed predominantly in renal medullary tubular cells, but not in glomeruli, and its receptor, VEGFR-1, is expressed in endothelial cells (51). Inhibition of VEGF-B can prevent the histological changes and renal dysfunction in diabetic mice, and particularly blocks the lipotoxicity of podocytes and improves insulin resistance (52).

Angiopoietins (Angs). Angs are a family of vascular growth factors that regulate vascular remodeling, maturation and stability. The Angs family includes Ang1, Ang2 and Ang4 (human homologous gene of mouse Ang3), and they interact with tyrosine kinase receptors (Tie1 and Tie2). Ang-Tie signaling is involved in different processes of vascular development and remodeling in different diseases. Angiotensin converting enzyme (ACE) also regulates vascular reactivity by regulating the production of nitric oxide (NO) (53,54).

In streptozotocin (STZ)-induced type 1 diabetic mice, the alteration of the milieu of vascular growth factors include a decrease in Ang1 levels, increase in VEGF-A levels, decrease in soluble VEGFR1 expression, and increase in phosphorylation of VEGFR2 (55). This alteration is accompanied by significant proteinuria, renal hypertrophy, hyperfiltration, ultrastructural changes of glomeruli and abnormal angiogenesis (55). Podocyte-specific inducible repletion of Ang1 can decrease proteinuria by 70% and prevent the proliferation of glomerular endothelial cells induced by diabetes (55). Ang2 levels are increased significantly in STZ-injected rat models and in diabetic patients (56).

Cartilage oligomeric matrix protein (COMP)-Ang1, a synthetic soluble, stable, and potent Ang1 variant, can phosphorylate the Tie2 receptor and Akt, and promote angiogenesis *in vitro* and *in vivo* (57). Lee *et al* (58) found that delivery of COMP-Ang1 in a type 2 diabetes model decreased mesangial dilation, basement membrane thickening and proteinuria, and significantly improved hyperglycemia (58). Ang1 redelivery increased ser1177 phosphorylation of endothelium nitric oxide synthase to maintain NO levels, and thus, the integrity of capillaries and endothelial cells (59,60). The overexpression of podocyte-specific Ang1 contributes to the stability of capillaries, in parallel to the decreased proliferation of glomerular endothelial cells in DN (55,61).

FGFs. It was suggested that FGF-1 has beneficial anti-inflammatory and renal protective activity *in vivo*. Recombinant FGF1 significantly inhibited renal inflammation, glomerular and tubular injury, and renal insufficiency in type I and II diabetic mice (62). FGF1 can correct the hyperglycemia in type II, but not in type I diabetic mice (62,63).

The administration of FGF21 can prevent renal lipid accumulation, oxidative stress, inflammation and fibrosis in mice after treatment with excessive fatty acids or STZ (64). The circular RNA, CIRC_0080425, significantly increased the expression of FGF11, through competitive binding with miR-24-3p, indirectly promoting DN (65). FGF21 negatively regulates the EMT process mediated by TGF-β-MDM2/Smad2/3 signaling by activating Akt/MDM2/p53 signaling pathway, so as to prevent renal fibrosis in DN (66). Conversely, in DN, serum FGF21 levels are associated with the severity of proteinuria and the rapid loss of glomerular filtration rate, which may be a biomarker of poor prognosis (67). Serum FGF21 levels are closely associated with the occurrence of nephropathy in type II diabetic patients, and is an independent predictor of functional renal loss (68). FGF21 is expressed in glomerular mesangial cells and in renal tubular epithelial cells of diabetic mice (69), and blocking the expression of FGF21 can aggravate fibrogenesis in mesangial cells induced by high glucose (70).

Diabetes-associated factors may affect plasma FGF23 levels, which are associated with the progression of CKD (71). High FGF23 levels seem to contribute to increased cardiovascular and mortality risks in type II diabetes patients, and this risk is significantly increased in DN (72).

Therefore, FGF/FGFR signaling in DN is more likely to induce fibrosis. Their role in angiogenesis is not direct, but instead mediated via regulation of members of the RTK family, such as Eph receptors and PDGFRs (73).

TGF-1β. In animal experiments, TGF-1 neutralizing antibodies and TGF-1 signal transduction inhibitor can effectively alleviate DN renal fibrosis (74). However, a clinical study of TGF-1 neutralizing antibodies failed to prove a sufficient effect on renal function in DN (74).

Angiogenesis inhibitors

Cell secretory proteins. (i) Pigment epithelium-derived factor (PEDF). PEDF was first purified from the human retinal pigment epithelial cells (75) and was further identified as a

member of the serine protease inhibitor (Serpin) family (76). Dawson *et al* (77) found that PEDF inhibited the proliferation of endothelial cells in a dose-dependent manner. Therefore, PEDF is regarded as the most potent endogenous angiogenesis inhibitor. Comparing the content of PEDF in the aqueous humor of patients with proliferative diabetic retinopathy (PDR) and non-PDRshowed that the levels of PEDF in the former significantlydecreased, which suggested that PEDF was the primary inhibitor of abnormal angiogenesis in human ocular tissues (78). Overexpression of PEDF in transgenic mice can effectively inhibit retinal neovascularization (79). PEDF expression is decreased in DN (80,81), and administration of recombinant PEDF protein successfully inhibits retinal neovascularization in a rat model of diabetes (82). The potential mechanism of PEDF may be associated with blocking of the Wnt signaling pathway (83), as inhibition of the Wnt/β-catenin signaling pathway can alleviate retinal vascular leakage and inhibit angiogenesis in diabetic rats (84). PEDF may also block p38 MAPK-GSK3-β-catenin signaling (85,86) and significantly decreased ATP production in agreement with direct binding to cell-surface ATP synthase to exert the anti-angiogenic activity (87). PEDF is able to block VEGF-induced angiogenesis via a γ-secretase-dependent pathway and by preventing dissociation of endothelial tight junction and adherens junction (88).

(ii) Kallikrein-binding protein (KBP/kallistatin). Kallikrein-binding protein (KBP), also termed *SERPINA3K*, was identified in human plasma as a Serpin (89). KBP is primarily synthesized and secreted by the liver, and it can bind to kallikrein in human tissues, inhibiting its function (90). KBP exerts pleiotropic effects on relaxation of blood vessels, and inhibits angiogenesis and antioxidative stress (90,91). Increased levels of circulating KBP are found in diabetic patients with microvascular complications (91), which is likely due to KBP binding with LRP6, thus inhibiting the proliferation of endothelial cells by antagonizing the classical Wnt signaling pathway (92). In an oxygen-induced retinopathy (OIR) model, KBP overexpression attenuated hypoxia-induced retinal angiogenesis and vascular permeability (93).

(iii) Thrombospondin (TSP)-1. The TSPs are a family of calcium-binding glycoproteins that are secreted by the majority of cell types and participate in transient or longer-term interactions with other extracellular matrix components, termed matricellular proteins. TSP-1 is primarily secreted by platelets, endothelial cells and tumor cells, and is present in the plasma and extracellular matrix. TSP-1 is regarded as a regulator of angiogenesis via interactions with αvβ3 integrin, MMP9, VEGF, FGF-2, MMP-2 and TIMP-2 (94). At the retinal level, TSP-1 supports retinal pigment epithelium cell structure and inhibits vascular endothelial cell adhesion (95). An *in vivo* study performed on Akita/+ male mice deficient in TSP-1 aggravated the pathological angiogenesis of diabetic retinopathy (96).

TSP-1 has specific cell surface receptors, including CD36 and CD47 (97). TSP-1/CD36 binding was shown to activate apoptosis by inducing p38 and Jun N-terminal kinase, and subsequently the cell-surface expression of Fas-L. Ligation of Fas by Fas-L stimulated a caspase cascade and ultimately apoptotic cell death (98). TSP-1/CD47 is an important factor mediating MWCNT-induced microvascular dysfunction, which disrupts •NO signaling and enhances leukocyte-endothelial interactions (99).

(iv) Soluble FMS-like tyrosine kinase-1 (sFLT-1). SFLT-1 is a soluble form of VEGFR-1, which can bind with VEGF-A, VEGF-B and is a powerful VEGF antagonist (100). Overexpression of sFLT-1 in podocytes of mice improves diabetic glomerulopathy and proteinuria (100). Overexpression of adeno-associated virus transduced sFlt-1 in db/db mice can decreasealbuminuria and improve podocyte injury (101). Adenovirus-mediated sFlt-1-induced proteinuria and glomerular endothelial proliferation similar to VEGF-A deficiency in mice (102).

(v) VASH-1. Vasohibin is an endothelium-derived negative feedback regulator of angiogenesis, which can be induced by VEGF in endothelial cells (103). Certain basic amino acid residues in the C-terminus of VASH-1 are important for heparin binding and its anti-angiogenic activities (104). The secretion and anti-angiogenic activity of VASH-1 requires the co-expression of small vasohibin-binding protein (105). The mechanism may be associated with the degradation of HIF-1α, which is mediated by prolyl hydroxylase (106). VASH-1 increases the stress tolerance of endothelial cells and promotes their survival (107). VASH-1 gene knockout can induce senescence of endothelial cells, which are prone to death due to cell stress (108), whereas overexpression of VASH-1 made endothelial cells resistant to premature aging and stress-induced cell death, and increased the expression of superoxide dismutase 2 and sirtuin 1 (108). The number of VASH-1-positive cells was positively associated with VEGFR-2 positive area and crescent formation (109). VASH-1 overexpression can significantly improve glomerular hypertrophy, glomerular filtration, proteinuria and glomerular endothelial area expansion in diabetic mice (18). Recombinant human VASH-1 also blocked high glucose-induced VEGFR-2 phosphorylation in a dose-dependent manner (18). Type I diabetes induced by STZ, increased proteinuria, glomerular hypertrophy, mesangial matrix accumulation and decreased diaphragmatic density in VASH-1 heterozygous mice (110). The positive area of glomerular CD31 and the expression of VEGF-A in kidney of VASH-1 heterozygous deficient mice was higher compared with diabetic wild-type mice (110). Endogenous VASH-1 may prevent angiogenesis of diabetic glomeruli and inflammation, as the anti-inflammatory effect of endogenous VASH-1 has also been confirmed in a unilateral ureteral obstruction model (111).

(vi) Matrix metalloproteinases (MMPs). MMP-7 expression is increased in the renal biopsy tissues of patients with diabetic nephropathy, and its levels are closely associated with the abundance of β-Catenin (112).

Hydrolytic fragments of precursor proteins

(i) Endostatin. Endostatin, a putative anti-angiogenic factor, is a 20-kDa proteolytic fragment of collagen XVIII (113). *In vitro*, it can inhibit the proliferation, migration and catheter formation of endothelial cells induced by VEGF (114). The interaction between endostatin and α5β1 integrin resulted in the inhibition

of FAK and the subsequent inhibition of MAPK (115). Endostatin inhibits glomerular VEGF-A primarily produced by podocytes in diabetic mice (116). In type I diabetic mice, endostatin significantly inhibited proteinuria and histological changes (116). The levels of circulating endostatin in patients with type II diabetic nephropathy is high, which suggests that endostatin may possess clinical value as a risk marker of diabetic nephropathy (117). Additionally, endostatin can decrease glomerular hypertrophy, hyperfiltration and proteinuria in STZ induced diabetic mice (116). Endostatin also significantly inhibits mesangial matrix expansion, extracellular matrix accumulation, endothelial cell proliferation and monocyte/macrophage infiltration (116). Anti-angiogenic endostatin polypeptide improves early renal lesions in a model of type I diabetic nephropathy (116). Circulating endostatin levels can predict progression and mortality of kidney disease, independently of established renal disease markers in type II diabetic patients (117).

(ii) Tumstatin. Tumstatin is derived from the type IV collagen α3 chain, which can inhibit pathological angiogenesis by inhibiting endothelial cell proliferation (118), by binding to the αVβ3 integrin of endothelial cells (119). Tumstatin acts as a specific inhibitor of endothelial cell protein synthesis through inhibition of the activation of FAK, protein kinase B (PKB/Akt), PI3-kinase and mammalian target of rapamycin (120). Tumor suppressor peptides significantly inhibited proteinuria and glomerular histological changes in diabetic mice, and increased the number of glomerular capillaries (121). Injection of tumstatin decreased glomerular hypertrophy, hyperfiltration and proteinuria in STZ-induced diabetic mice (121). It also inhibited the increase in the levels of VEGF-A and VEGFR-2 in kidneys induced by diabetes (121). Due to the high expression of αVβ3 integrin in podocytes (122), the primary target of tumstatin may not be endothelial cells, but instead podocytes.

(iii) Angiostatin/Kringle1-4. Angiostatin is a protective fragment of plasminogen, which can inhibit tumor angiogenesis (123). Adenovirus mediated angiostatin can significantly improve proteinuria and glomerular hypertrophy in type I diabetic rats (124). In a model of CKD induced by a subtotal nephrectomy, angiostatin treatment decreased the number of peritubular capillaries and urinary nitric oxide levels (125). *In vitro*, angiostatin decreased the upregulated expression of VEGF and TGF-β in human mesangial cells induced by high glucose, and increased the levels of pigment epithelium-derived factor, an endogenous DN inhibitor (124).

(iv) Kringle5 (K5). K5 is the fifth domain of human plasminogen associated with angiostatin (K1-4). Its molecular weight is only 16 kDa and it is the most active anti-angiogenic fragment in human plasminogen (126). In an OIR and STZ-induced rat model, K5 inhibited retinal neovascularization (127). Additionally, K5-induced endothelial cell apoptosis was shown to be mediated by a positive feedback loop involving VDAC1-AKT-GSK3β-VDAC1 (128), which resulted in inhibition of angiogenesis.

Others. Netrin-1 and UNC5B were shown to be upregulated in STZ-induced rats, and UNC5B upregulation contributed partly to enhancing angiogenesis in DN (129). PDE5 inhibitors exert protective effects by improving perivascular inflammation through modulating miR-22 and BMP7 in a DN mouse model (130). The Slit2/Robo1 signaling pathway is involved in angiogenesis of glomerular endothelial cells in a diabetic-like environment (131). Neurite outgrowth inhibitor-B serves an important role in vascular remodeling, which protects the vasculature system in a model of DN (132).

Angiogenesis vs. vasculogenesis. Angiogenesis is the process by which fewer blood vessels branch and bud to form off shoot vessels. Vasculogenesis is the process in which endothelial cells differentiate from endothelial progenitor cells to connect and form a tube, ultimately resulting in the formation of new blood vessels.

3. Clinical and anti-angiogenic treatment

The early diagnosis of DN (stage I DN) includes thickening of the glomerular basement membrane and renal tubular basement membrane, whereas after glomerular thickening, the mesangial cell dilation is considered stage II DN (133). The expansion of the mesangium further leads to glomerular leakage combined with the accumulation of fibronectin and type IV collagen, which also leads to nodular sclerosis (stage III DN) (133). Increased potassium secretion and angiogenesis signals are early renal responses in human DN (134).

Renin angiotensin enzyme inhibitors (such as ACEI or ARB) should be administered as soon as possible, as both of these can decrease systemic and intraglomerular blood pressure by inhibiting the action of ACEII on angiotensin II type 1 receptor (AT1) receptor (1). ACEI lowers the production of angiotensin II (135), whereas the AT1 antagonists block the AT1 receptor (136). It has been reported that proteinuria and hypertension are common complications (137). In nodular diabetic glomerulopathy, there are vascular mesangial channels, which serve as indicators of the changes in neovascularization and blood flow in these glomeruli (138). Nilotinib hydrochloride is a highly potent tyrosine kinase inhibitor that can inhibit the progress of DN via the regulation of a variety of mechanisms (139).

It has been shown that promoting anti-angiogenesis (particularly via anti-VEGF mechanisms) may be a promising strategy for management of the early stages of DN, based on several animal experiments (1). However, there are currently no anti-VEGF-A based treatments for patients with DN. In some studies, patients with DN who received intravitreal injection of VEGF-A inhibitors have shown contrasting results; that is renal damage associated with glomerular microangiopathy, including thickening of the capillary wall and glomerular basement membrane (140), or rapidly worsening proteinuria and decreased kidney function (141). Therefore, therapies involving anti-VEGF-A in DN should first aim to maintain physiological levels of VEGF-A. Otherwise, excessive inhibition of VEGF-A may cause harmful side effects. Recently, a study on patients with early DN showed that intravitreal injection of bevacizumab resulted in worsening proteinuria and renal function, and this was improved using ranibizumab, which had a lower potency (13).

The vasohibin family may participate in mesangial expansion by mediating VEGFR2 signaling. Current studies indicate

Table I. Summary of proangiogenesis and antiangiogenesis factors.

A, Proangiongenesis factors

Factors	Animal model	Treatment (gene modulation or drugs dose)	Results	Mechanisms
VEGF-A	db/db mice (24) (T2D)	SU5416 (24), 2 mg/kg	Ameliorated diabetic albuminuria	Pan-VEGF receptor tyrosine kinase inhibitor
	STZ-induced mice (T1D) and db/db mice (T2D)	Anti-VEGF Ab (16,25,26) (dose varied)	Decreased proteinuria and glomerular hypertrophy	Neutralizes the VEGF
	T1D rat model (uninephrectomized+STZ)	RSV (27), 20 mg/kg	Lowered the increases in glomerular diameter, mesangium accumulation, glomerular basement membrane thickness and renal fibrosis	Decreased VEGF
	Adult transgenic mice	Overexpression of *VEGF-A* in podocytes (41)	Proteinuria, glomerular enlargement, glomerular basement membrane thickening, mesangial expansion and podocyte disappearance	
	Adult mice	VEGF-A gene deletion in podocytes (40)	Increase in proteinuria, thrombus and capillary ring occlusion in capillaries, endothelial cell swelling	Decreased VEGF
Angs	STZ-induced mice (T1D)	Podocyte-specific inducible repletion of Ang1	Decreased proteinuria by 70% and prevents the proliferation of glomerular endothelial cells (55)	DecreasingAng1 levels
	STZ-induced rat models (T1D)			IncreasedAng2 (56)
	db/db mice (T2D)	Ade-COMP-Ang1, X109 PFU of (58)	Decreased mesangial dilation, basement membrane thickening and proteinuria, and significantly improved hyperglycemia	Ang1 redelivery increased ser1177 phosphorylation of endothelium nitric oxide synthase (eNOS) to maintain NO level and integrity of capillaries and endothelial cells (59,60)

B, Antiangiongenesis factors

Factors	Animal model	Treatment (gene modulation or drugs dose)	Results	Mechanisms
PEDF	Transgenic mice and OIR model	Overexpression of PEDF	Inhibited retinal neovascularization (79)	
	STZ-induced rat models (T1D) and OIR rat model	rPEDF protein, 1.5 μg/eye (82)	Inhibited retinal neovascularization	Wnt signal blocking (83) p38MAPK-GSK3-β-catenin signalblocking (85,86). VEGF-induced angiogenesis blocking (88).

Table I. Continued.

B, Antiangiongenesis factors

Factors	Animal model	Treatment (gene modulation or drugs dose)	Results	Mechanisms
KBP	OIR and Akita mice models (93) (T1D)	KBP overexpression	Attenuated hypoxia-induced retinal angiogenesis and vascular permeability (93)	Suppressed Wnt pathway activation (92)
TSP-1	Akita/+ TSP1-/- male mice	Deficient in TSP-1	Pathological angiogenesis of diabetic retinopathy	Interacts with αvβ3 integrin, MMP9,VEGF, FGF-2, MMP-2 and TIMP-2 (94). TSP-1/CD36 activated apoptosis (98). TSP-1/CD47 mediatedMWCNT-induced microvascular dysfunction (99).
sFLT-1	db/db mice (T2D)	Overexpression of sFLT-1 in podocytes	Improved diabetic glomerulopathy and proteinuria (101)	SFLT-1 is a soluble form of VEGFR-1, which can bind with VEGF-A, VEGF-B, and is a powerful VEGF antagonist (100)
	Pregnant and non-pregnant Balb/c mice	Adenovirus-mediated sFlt-1	Glomerular endothelial proliferation (102)	
VASH-1	STZ-induced mice (T1D)	VASH-1 overexpression (18)	Improved glomerular hypertrophy, glomerular filtration, proteinuria and glomerular endothelial area expansion.	Degradation of hypoxia inducible factor-1α (HIF-1α) mediated by prolyl hydroxylase (106) blocked high glucose-induced VEGFR-2 phosphorylation (18)
	STZ-induced mice (T1D)	VASH-1 heterozygous mice	Increased proteinuria, glomerular hypertrophy, mesangial matrix accumulation and decreased diaphragmatic density (110)	
Endostatin	STZ-induced mice (T1D)	Endostatin peptide treatment (1or 5 mg/kg body wt) (116)	Glomerular hypertrophy, hyperfiltration, and albuminuria were significantly suppressed by endostatin peptide (5 mg/kg)	Inhibited glomerular VEGF-A mainly produced by podocytes in diabetic mice
Tumstatin	STZ-induced mice (T1D)	Tumstatin-peptide (T8-peptide) at the dosage of 1 mg/kg (121)	Decreased glomerular hypertrophy, hyperfiltration and proteinuria	Inhibited pathological angiogenesis by inhibiting endothelial cell proliferation through inhibiting the activation of FAK, PI3K, PKB/Akt, and mTOR (120)
Angiostatin	STZ-induced rats (T1D)	Adenovirus-mediated angiostatin (124)	Significantly alleviated albuminuria and attenuated the glomerular hypertrophy	Angiostatin downregulated the expression of VEGF and TGF-β1 (124)
	Subtotal nephrectomy CRD model	Angiostatin treatment (125)	Decreased renal peritubular capillary number and decreased urinary nitric oxide levels	
K5	OIR and STZ-induced rat model		K5 inhibits retinal neovascularization (127)	K5-induced endothelial cell apoptosis is mediated by the positive feedback loop of 'VDAC1-AKT-GSK3β-VDAC1' (128)

VEGF, vascular endothelial growth factor; STZ, streptozotocin; RSV, resveratrol; Angs, angiopoietins; COMP, cartilage oligomeric matrix protein; OIR, oxygen-induced retinopathy; PEDF, pigment epithelium-derived factor; KBP, kallikrein-binding protein; TSP-1, thrombospondin 1; FGF, fibroblast growth factor; MMP, matrix metalloproteinase; TIMP, tissue inhibitor of metalloproteinases; MWCNT; sFLT-1, soluble FMS-like tyrosine kinase-1; VASH-1, vasohibin 1; FAK, focal adhesion kinase; K5, Kringle 5; VDAC1, voltage-dependent anion channel 1; T1D, type I diabetes; T2D, type II diabetes.

that the vasohibin family may be a promising therapeutic target to reduce excessive angiogenesis and renal fibrosis in DN, however, further research is required to understand their relevance and clinical significance.

4. Other diabetic microvascular complications and treatments

Other diabetic microvascular complications include diabetic retinopathy, erectile dysfunction, macular oedema (DMO) and diabetic foot. Diabetic patients with retinal microvascular lesions, pericytes necrosis, endothelial barrier function damage and blood components from the blood vessels in the tissue, result in retinal lesions and dysfunction. This may be due to the fact that high glucose can induce the apoptosis of pericytes in diabetic retina, damaging the blood retinal barrier and activating vascular endothelial cells, thus promoting vascular budding and angiogenesis. Almost all cells in the retina can secrete VEGF under the stimulation of ischemia and hypoxia. A large amount of clinical data has shown that VEGF levels in the vitreous cavity of patients with PDR is significantly increased (142). Treatments include panretinal photocoagulation, intravitreal injection of bevacizumab, aflibercept or ranibizumab, and surgery. Resveratrol may improve diabetic retinopathy by regulating the expression of PEDF and TSP-1 (143). PDE5 inhibitors (such as sildenafil and tadalafil) are currently used in the treatment of diabetic erectile dysfunction. PDGF can promote cell migration and smooth muscle proliferation and accelerate wound healing (144). In addition, recombinant VEGF (145), EGF (146), FGF (147), TGF-β (148) and IGF-1 (149) can be used treatment of diabetic foot. DMO is a common complication of diabetic retinopathy, and antiangiogenic therapy with anti-VEGF can decreaseoedema, improve vision and prevent further visual loss (150).

Acknowledgements

Not applicable.

Funding

This work is supported by Yunnan Fundamental Research Projects (grant no. 202001AT070145).

Availability of data and materials

Not applicable.

Authors' contributions

QRT drafted the majority of the review. YMC contributed to drafting the review. LW revised the review. CT conceptualized the review. YYH participated conceptualizing and designing the review, and participated in drafting and reviewing the review. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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