Endothelial dysfunction: A central mechanism linking autosomal dominant polycystic kidney disease and intracranial aneurysms (Review)

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Abstract. Autosomal dominant polycystic kidney disease (ADPKD) is the most common hereditary kidney disorder and is characterized by the progressive development of multiple bilateral renal cysts and the deterioration of renal function. Patients with ADPKD also have a substantially elevated risk of diverse systemic vascular complications such as intracranial aneurysm (IA), a serious life-threatening condition. IA occurs much more frequently in patients with ADPKD than in the general population, and IA rupture can lead to subarachnoid hemorrhage, a major cause of mortality and long-term disability. Although clinical evidence supports an association between ADPKD and IA, the exact nature of the molecular and pathological connections between these conditions remains unclear, making it difficult to develop effective preventive and therapeutic strategies. Advances in vascular biology have led to the view that endothelial dysfunction is a pivotal event in the pathogenesis of multiple vascular diseases. Consequently, there is increasing attention on the role of endothelial dysfunction in mediating the relationship between ADPKD and IA. The present review first summarizes the physiological functions and structural characteristics of endothelial cells, and then focuses on the pathological effects of endothelial dysfunction in ADPKD and IA. Additionally, the review describes therapeutic strategies that aim to restore endothelial function, with a focus on the use of early screening and precision treatment, to improve the prognosis of patients with ADPKD complicated by IA.

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Contents

1. Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is a hereditary disorder caused by mutations in the polycystic kidney disease (*PKD*)*1* or *PKD2* genes. Its global prevalence ranges from 1/400 to 1/1,000 (1) and it is the leading monogenic cause of chronic kidney disease (CKD) (2,3). The pathological manifestations of ADPKD are systemic, in that the progressive enlargement of renal cysts can affect multiple systems, particularly the cardiovascular and digestive systems (3). Vascular complications, such as intracranial aneurysm (IA), are critical determinants of the prognosis of patients with ADPKD (4). IA is a potentially life-threatening cerebrovascular lesion characterized by localized dilation or bulging of the intracranial arterial wall (4). The rupture of an IA results in subarachnoid hemorrhage, which is associated with a mortality rate of 30 to 50% and permanent neurological deficits in ~50% of survivors (4,5).

Clinical studies have unequivocally established that patients with ADPKD have a high risk for IA (6-8). Relative to the general population, IA in patients with ADPKD has a significantly higher incidence and an earlier age of onset, and the aneurysms are larger and have an increased risk of rupture (9). A multicenter cohort study of more than 2,000 patients with ADPKD reported that IA had an overall

incidence of approximately 8 to 10, and >15% in patients with hypertension or a family history of IA (8). This clinical observation strongly suggests an underlying pathological association between ADPKD and IA; however, the molecular mechanisms and pathological pathways mediating this association remain poorly understood (6,10).

Previous research has primarily focused on the indirect effects of systemic factors, such as hypertension and renal dysfunction, on cerebrovascular integrity in patients with ADPKD (11). However, these factors alone are insufficient to fully explain the high prevalence of IA in patients with ADPKD (12). More evidence has validated the central role of endothelial dysfunction in the pathogenesis of cardiovascular diseases (13). Examination of endothelial dysfunction provides a novel perspective for elucidating the relationship of ADPKD and IA, because it provides a key pathological link that integrates genetic defects, environmental factors, and vascular lesions (14). Endothelial cells act as the interface between the vascular wall and the bloodstream, and they maintain vascular tone, barrier function, and overall homeostasis through a complex molecular regulatory network (15). Mutations in the *PKD1* and *PKD2* genes may directly disrupt this regulatory network by inducing endothelial dysfunction and promoting the development and progression of IA (12).

Building on these observations, the present review systematically analyzes the pathological basis and mechanisms of endothelial dysfunction in ADPKD. It describes the critical role of endothelial dysfunction in the pathogenesis of IA and clarifies this dysfunction as a key pathological bridge between ADPKD and IA. Furthermore, the review explores therapeutic strategies and clinical challenges that have focused on restoring endothelial function. Our broader purpose is to provide comprehensive theoretical support for basic research and clinical interventions that seek to improve the management of patients with ADPKD complicated by IA.

2. Mechanism of endothelial dysfunction

The endothelium is a monolayer of flattened cells lining the inner surface of blood vessels that functions as a dynamic interface between the vascular wall and bloodstream (16). Beyond its role as a physical barrier, the endothelium is as a crucial endocrine and paracrine organ that functions in numerous physiological processes (17): i) It regulates vascular tone by modulating the contraction and relaxation of vascular smooth muscle cells (VSMCs) (18). These cells secrete vasodilators [such as nitric oxide (NO) and prostacyclin] and vasoconstrictors (including endothelin and angiotensin II) that help to maintain homeostasis (19). Specifically, endothelial nitric oxide synthase (eNOS) synthesizes NO, which then activates guanylate cyclase in VSMCs. The resulting increase in cyclic guanosine monophosphate drives the relaxation of VSMCs and maintains normal hemodynamics (20,21). ii) It maintains vascular permeability by forming a barrier via tight and adherens junctions which regulate the transport of nutrients and immune cells (22). The structural integrity of tight junction proteins, such as zonula occludens-1, directly affects the permeability of the endothelial barrier (23). iii) It inhibits thrombosis and platelet aggregation by releasing prostacyclin and NO, expressing anticoagulant molecules, and promoting fibrinolysis, thereby preserving normal blood flow (24). iv) It regulates inflammatory responses by expressing adhesion molecules, such as selectins and integrins. This mediates leukocyte adhesion to the vascular wall and initiates the inflammatory cascade (24). v) It is the primary effector of angiogenesis, in that endothelial cells proliferate and migrate after stimulation by growth factors. The participation of these cells in vascular formation and regeneration is essential for maintaining tissue perfusion (24).

The functional integrity of endothelial cells depends on their structural stability and homeostatic regulatory networks, particularly mechanosensory responses and calcium homeostasis (25). Membrane-localized protein complexes and intracellular signaling pathways coordinate these physiological functions (25). Endothelial cells have primary cilia, solitary, immotile, microtubule-based organelles which project into the vascular lumen, that are mechanosensors which detect fluid shear stress. Under normal physiological conditions, blood-flow-induced ciliary deflection activates mechanotransduction pathways and promotes flow-dependent intracellular calcium signaling. Calcium, a key intracellular messenger, regulates vascular tone, permeability, and inflammatory responses by activating downstream pathways, such as NO synthesis (26). Consequently, abnormal calcium signaling in endothelial cells directly impairs these critical functions (27).

Multiple etiological factors can impair the normal physiological function of the endothelium. A dysfunctional endothelium is characterized by alterations such as decreased vasodilatory capacity, increased vascular permeability, decreased antithrombotic activity, and aberrant activation of inflammation (28). Endothelial dysfunction is a pivotal initial event in the pathogenesis of multiple vascular disorders, and is predominantly driven by interactions of hemodynamic disturbances, oxidative stress, inflammatory activation, overactivation of the renin-angiotensin-aldosterone system (RAAS), genetic defects, and aging (Fig. 1) (29,30).

A stable hemodynamic microenvironment is essential for maintaining endothelial homeostasis, whereas hemodynamic abnormalities, such as disruptions caused by shear stress, are a key determinant of endothelial dysfunction (31). Shear stress refers to the frictional force exerted by blood flow on the luminal surface of endothelial cells (32). Under normal physiological conditions, laminar shear stress activates endothelial mechanoreceptors, and this promotes the synthesis and release of NO and maintenance of normal vascular function (33). By contrast, pathological conditions are characterized by a shift from laminar flow to turbulent flow or low shear stress, and these can trigger endothelial cells to adopt a pro-inflammatory phenotype (34) with decreased NO synthesis, that ultimately impairs vascular function (35).

Oxidative stress is a core driver of endothelial dysfunction, in that an excessive level of reactive oxygen species (ROS) directly damages endothelial cells. This leads to a self-reinforcing cycle, because elevated ROS levels deplete the availability of NO, and this further exacerbates endothelial injury (13). Specifically, ROS disrupt the structural integrity of endothelial cells and interfere with multiple signaling pathways, including those that regulate vascular tone and inflammation, and this impairs the overall function of the endothelium (36,37).

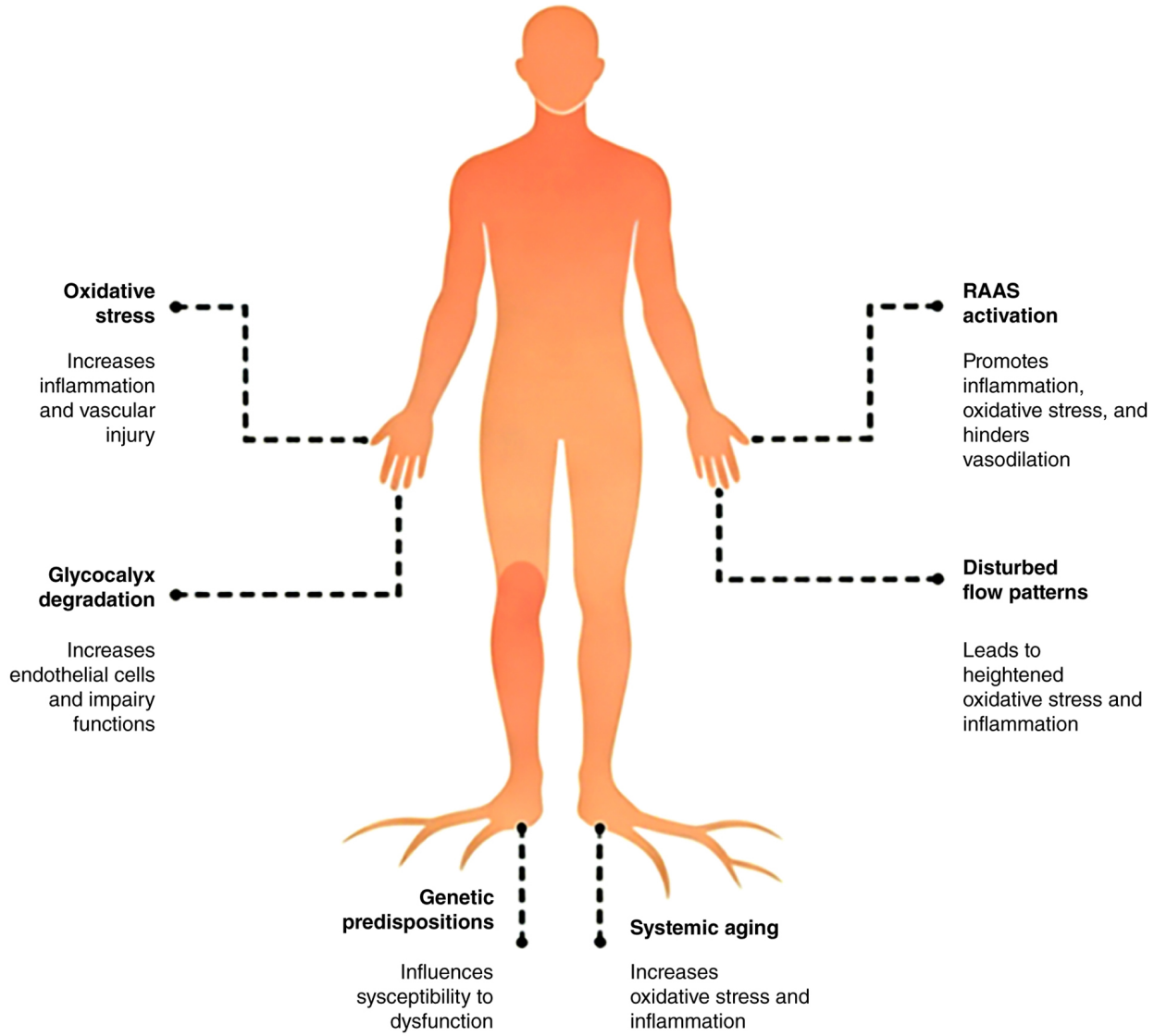

Figure 1. Multiple factors promote endothelial dysfunction. The pathogenesis of endothelial dysfunction can be conceptualized as a 'tree', in which distinct stimuli in the 'roots' lead to endothelial injury and systemic dysfunction in the 'branches'. The 'roots' consist of genetic predispositions, which increase susceptibility to dysfunction, and systemic aging, which increases oxidative stress and inflammation. The 'branches' include glycocalyx degradation, which impairs the integrity of the endothelial barrier and promotes leukocyte adhesion and vascular injury; oxidative stress, which damages endothelial cells, decreases the production of NO, and disrupts vascular homeostasis; disturbed flow patterns, which activate endothelial cells via shear stress, and increase vascular permeability and the infiltration of leukocytes; and activation of the RAAS, which exacerbates vasoconstriction, oxidative stress, and systemic inflammation. RAAS, renin-angiotensin-aldosterone system.

Inflammatory responses and endothelial dysfunction are thus part of a positive feedback loop: Inflammatory activation increases endothelial dysfunction, and endothelial dysfunction increases inflammatory signaling (38). At the molecular level, activated endothelial cells secrete various chemokines that recruit inflammatory cells, and this aggravates local inflammation and further impairs vasodilatory function and vascular permeability (39).

The RAAS is a critical endocrine system that regulates blood pressure and fluid homeostasis, and inappropriate activation is closely associated with endothelial dysfunction (40). RAAS activation begins with increased secretion of renin, an enzyme that catalyzes the conversion of angiotensinogen to angiotensin I (Ang I) (41). Angiotensin-converting enzyme then converts Ang I to angiotensin II (Ang II), which binds to cognate receptors on target cells and promotes diverse biological responses (42). Ang II impairs endothelial function through several mechanisms (43). First, it activates NADPH oxidase (NOX) in endothelial cells to produce ROS, and this triggers oxidative stress, impairs eNOS activity, and decreases NO synthesis (44). Second, it activates inflammatory signaling pathways, such as the nuclear factor-κB (NF-κB) pathway, and this induces the expression of adhesion molecules and pro-inflammatory cytokines, thereby exacerbating inflammation (44). Third, it directly disrupts endothelial cell tight junctions, and this increases vascular permeability, the proliferation and migration of VSMCs, and vascular remodeling (45).

Genetic defects can also contribute to endothelial dysfunction (46) by disrupting the regulation of endothelial cell signaling or the structural integrity of these cells, leading to functional abnormalities (47). For instance, mutations in the

PKD1 or *PKD2* genes of patients with ADPKD are associated with endothelial dysfunction in these patients (12). Advanced age is associated with decreased endothelial function (48). This association may be mediated, at least in part, by endothelial cell senescence, reduced regenerative capacity, increased oxidative stress, and chronic low-grade inflammation (46). In summary, multiple interacting biological factors can lead to endothelial dysfunction and lead to the onset or increase the progression of different vascular diseases.

3. Endothelial dysfunction in ADPKD

ADPKD follows an autosomal dominant inheritance pattern, with a 50% probability of disease transmission to offspring (47), and is caused by mutations in the *PKD1* or *PKD2* gene (49). Notably, ~85% of these patients harbor *PKD1* mutations and 15% have *PKD2* mutations (50). The pathological progression of ADPKD is highly heterogeneous, although numerous patients develop renal cysts during early adulthood (51). The number and volume of these cysts increase over time, and patients eventually develop a progressive decline of renal function (52). Of note, ~50% of patients progress to end-stage renal disease by the age of 60 and require dialysis or kidney transplantation for survival (53).

ADPKD also affects multiple organ systems beyond the kidneys. Notably, it can lead to cardiovascular complications, such as hypertension and heart failure, that severely impact quality of life (54). Hypertension is a common early complication of ADPKD, with an incidence of 60 to 80%, that is attributable to renal cyst compression and activation of the RAAS (55). Uncontrolled long-term hypertension can damage the vascular endothelium and increase the risk of cardiovascular complications (56). Additionally, patients with ADPKD often develop structural abnormalities of the vascular walls, and this promotes the progression of vascular complications (57).

IA is a severe cerebrovascular disorder that has a significantly higher incidence than ADPKD (~3.2% vs. 0.1%) and an earlier age at onset than ADPKD. ADPKD increases the risk for IA, and these patients tend to have larger aneurysms and an increased risk of rupture compared with patients with IA without ADPKD (58). The high incidence of IA in patients with ADPKD is closely associated with the genetic background of patients, endothelial dysfunction, and hypertension, and endothelial dysfunction is a key pathological link between ADPKD and IA (14).

The *PKD1* and *PKD2* genes encode the polycystin 1 (PC1) and PC2 proteins, which play key roles in maintaining the function of the vascular endothelium (59). PC1 is a complex transmembrane glycoprotein that has 4,302 amino acids, a large extracellular N-terminal domain, and 11 transmembrane domains (59). PC2 is a 968-amino-acid protein in the transient receptor potential ion channel family that contains 6 transmembrane domains (60). These two proteins interact via their carboxyl-terminal ends to form a heterotetrameric complex that functions in the homeostasis of endothelial calcium (61). Endothelial primary cilia are solitary, immotile, microtubule-based organelles that project into the vascular lumen and act as mechanosensors. Under normal physiological conditions, blood-flow-induced shear stress deflects these cilia, activates PC1/PC2-associated mechanotransduction, and triggers intracellular calcium signaling (32).

This calcium signaling is crucial for endothelial function, regulation of eNOS activity, maintenance of endothelial cell tight junctions, and regulation of cell proliferation, migration, and apoptosis (62). PC1 also helps to maintain the structural stability of the endothelium due to its interactions with various signaling and cell adhesion molecules (60).

Previous studies have identified more than 1,000 different *PKD1* mutations in ADPKD, including missense mutations, nonsense mutations, deletions, insertions, and splice site mutations (12). These mutations can cause structural abnormalities in the PC1 protein or complete loss of expression, thereby preventing formation of the PC1/PC2 complex and disrupting calcium homeostasis in endothelial cells (63). The impact of different mutations on the function of the PC1/PC2 complex varies significantly: Some prevent localization of PC1 to the cell membrane; some decrease the activity of calcium ion channels; and some lead to protein instability (64). Advances in gene sequencing technology have led to identification of an increasing number of novel *PKD1* mutations (65). For example, the NM_000296.4:c.10086G>T mutation significantly impairs localization of PC1 to the plasma membrane and calcium-mediated signal transduction, resulting in a blunted intracellular calcium response (65). Furthermore, cells carrying this mutation exhibit dysfunctional angiogenesis and impaired vascular barrier function. Research findings that link *PKD1* mutations with endothelial dysfunction provide a pathological basis for vascular complications in ADPKD (66). Other *PKD1* mutations drive endothelial dysfunction by similar mechanisms (14).

Disruption of calcium signaling caused by mutations of *PKD1* or *PKD2* induces endothelial dysfunction primarily by decreasing NO synthesis, activating oxidative stress and inflammatory responses, and promoting endothelial-to-mesenchymal transition (EndMT) (67). The interactions of these pathways accelerate the decline of endothelial function (Fig. 2) (68).

NO is a key vasodilator derived from endothelial cells whose synthesis and release require the activation of eNOS, which is regulated by calcium signaling (69). In healthy endothelial cells, stimuli such as shear stress and acetylcholine activate the PC1/PC2 complex (70). This activation increases the level of intracellular calcium and activates eNOS to catalyze the conversion of L-arginine to NO, which then mediates vasodilation (71,72). However, mutations in the *PKD1* or *PKD2* genes impair PC1/PC2 function, disrupt calcium-mediated signal transduction, decrease eNOS activity, and decrease the production of NO (73). These changes compromise vasodilatory function and can contribute to the pathogenesis of hypertension and IA (74).

Disruption of calcium signaling also promotes oxidative stress in endothelial cells by upregulating NOX activity and impairing mitochondrial function, responses that lead to the overproduction of ROS (75,76). These elevated levels of ROS damage endothelial cells, activate inflammatory signaling pathways, and promote the release of inflammatory mediators. These responses exacerbate endothelial injury and lead to a self-amplifying cascade of vascular damage (77).

EndMT is a pathological process in which endothelial cells develop into a mesenchymal phenotype, leading to a loss of

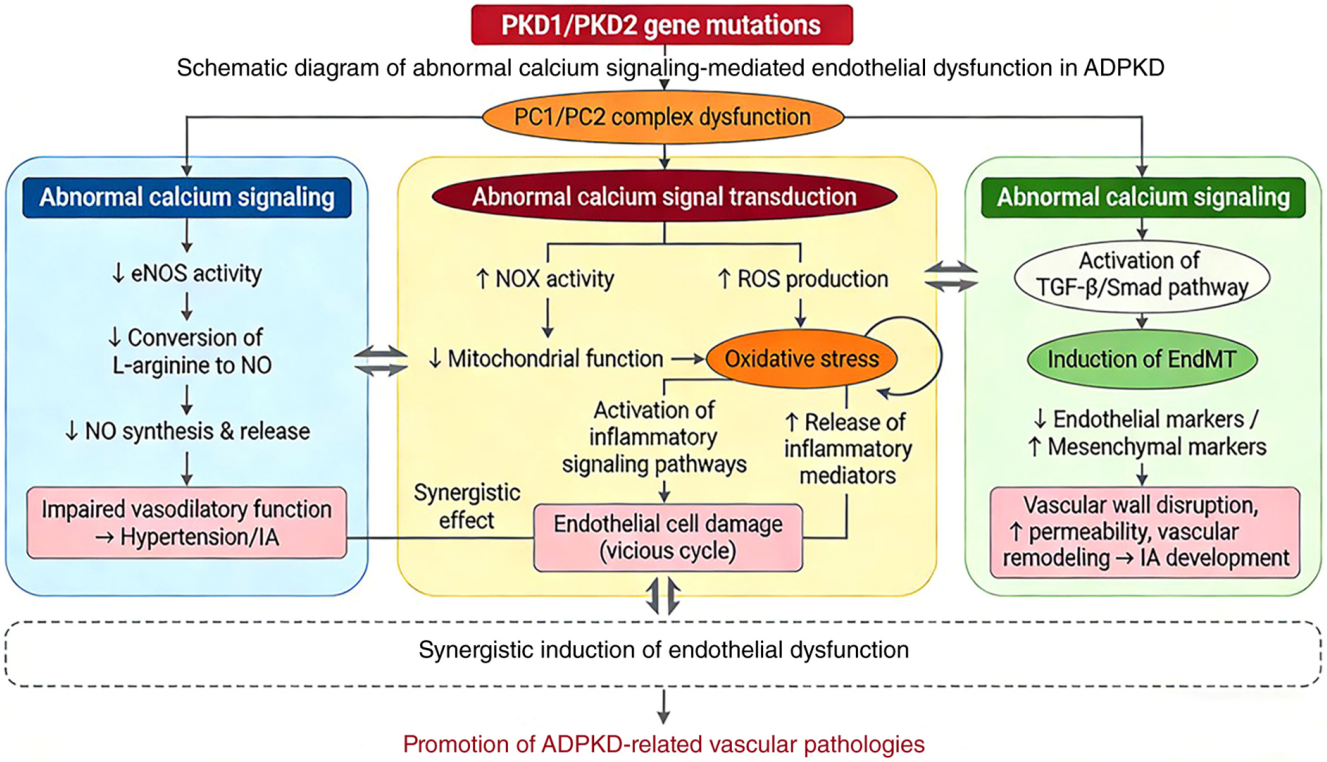

Figure 2. Abnormal calcium signaling increases endothelial dysfunction in ADPKD. Mutations in *PKD1* or *PKD2* impair the function of the PC1/PC2 complex and disrupt calcium signal transduction in endothelial cells. This disrupted calcium signaling induces endothelial dysfunction by decreasing NO synthesis, increasing oxidative stress and inflammation, and inducing EndMT. Collectively, these alterations lead to endothelial dysfunction, which can lead to hypertension and development of an IA. ADPKD, autosomal dominant polycystic kidney disease; *PKD1*, polycystic kidney disease 1; *PKD2*, polycystic kidney disease 2; PC1, polycystin 1; PC2, polycystin 2; NO, nitric oxide; EndMT, endothelial-to-mesenchymal transition; IA, intracranial aneurysm; eNOS, endothelial nitric oxide synthase; NOX, NADPH oxidase.

endothelial integrity and driving vascular remodeling (78). In ADPKD, abnormal calcium signaling can induce EndMT via activation of the transforming growth factor-β (TGF-β)/Smad signaling pathway (79). This activation is associated with the downregulation of endothelial cell markers and the upregulation of mesenchymal markers (80). This is followed by alterations in the vascular wall, increased endothelial permeability, and an acceleration of pathological remodeling, changes that can provide a structural foundation for the development of IA (80).

4. Endothelial dysfunction in the pathogenesis of IA

An IA is a saccular bulge caused by structural abnormalities or damage to the intracranial arterial wall (81). Its pathogenesis involves a progressive decline in structural integrity of the vascular wall, which consists of the intima, media, and adventitia, due to the disruption of endothelial homeostasis (82,83). The elastin and collagen fibers in the media are critical for maintaining the elasticity and structural integrity of the vascular wall (84). The structure and function of the vascular wall depend on a dynamic balance among endothelial cells, VSMCs, extracellular matrix (ECM), and cytokines (85). Several key processes contribute to this balance, including regulation of vascular tone by endothelial and VSMCs and synthesis of the ECM (86). Disruption of this balance leads to structural and functional abnormalities of the vascular wall that can lead to the formation of an aneurysm (87). IA development is a multifactorial and multi-step process driven by key pathological alterations, such as a dysfunctional endothelium, infiltration of inflammatory cells, and degradation of the ECM (88). Among these, a dysfunctional endothelium is considered to initiate the pathogenesis of IA (89).

Endothelial dysfunction can initiate IA due to its disruption of the integrity of the vascular barrier, dysregulation of VSMCs, and exacerbation of oxidative stress and inflammatory responses (Fig. 3) (90).

A healthy endothelial barrier has an intact and functional vascular wall, but a dysfunctional endothelial barrier is characterized by increased vascular permeability (91) because damage of the endothelial tight junctions allows plasma proteins and inflammatory cells to infiltrate the vascular wall (92). After infiltration, inflammatory cells release cytokines that stimulate matrix metalloproteinases (MMPs) to degrade the ECM (93). This degradation of the vascular wall decreases its compliance and strength, and can lead to the formation of an aneurysm (94).

VSMCs play a crucial role in maintaining the structure and function of the vascular wall (95). Endothelial dysfunction impairs the activity of VSMCs, leading to a dysfunctional vascular tone (96). The switching of VSMCs to a synthetic phenotype, characterized by increased proliferation and migration but decreased synthesis of the ECM, significantly decreases vascular compliance (97). Additionally, the oxidative stress and inflammatory responses triggered by endothelial dysfunction promote the apoptosis of VSMCs (98), and this

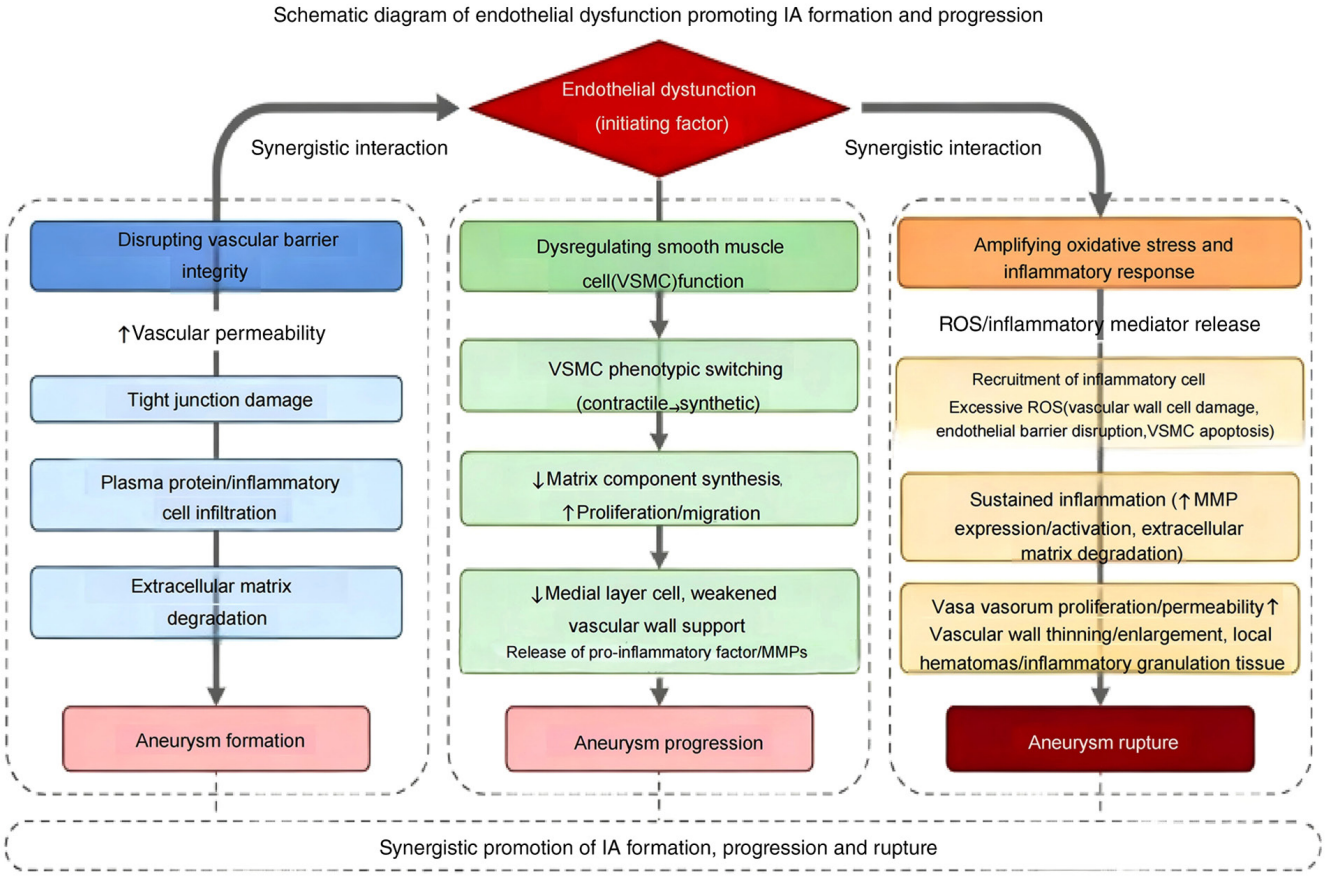

Figure 3. Endothelial dysfunction promotes the formation and progression of IA. Endothelial dysfunction initiates and promotes the progression of IA by disrupting the integrity of the vascular barrier, dysregulating VSMCs, and increasing oxidative stress and inflammation. IA, intracranial aneurysm; VSMCs, vascular smooth muscle cells; MMP, matrix metalloproteinase.

decreases the number of medial layer cells and weakens vascular wall support (99). The apoptosis of VSMCs also leads to increased local levels of pro-inflammatory cytokines and MMPs (100). These processes further increase inflammation and degradation of the ECM, creating a highly destructive positive feedback loop that leads to increasing impairment of vascular wall compliance, decreasing structural support (101), and progression of an aneurysm (102).

Endothelial dysfunction also increases oxidative stress and inflammatory responses, and this self-amplifying cascade leads to increased damage of vascular walls and growth of an aneurysm toward eventual rupture (103). ROS and inflammatory mediators released by endothelial cells recruit additional inflammatory cells, thus intensifying local inflammation (104). The excessive production of ROS damages cells in the vascular walls, disrupts the endothelial barrier, and inhibits the proliferation of VSMCs and the synthesis of the matrix. These changes culminate in the apoptosis of VSMCs (105). These sustained inflammatory responses also induce the expression and activation of MMPs, and this promotes degradation of the ECM, thinning of the vascular wall, and enlargement of the aneurysm (106). Moreover, proliferation and increased permeability of the vasa vasorum can lead to the formation of local hematomas or inflammatory granulation tissue, further compromising the integrity of the vascular wall (106). When oxidative stress and inflammatory responses reach a critical level, damage of the aneurysm wall can become so severe that it ruptures (107).

The high incidence of IA in patients with ADPKD is closely linked to the endothelial dysfunction caused by the *PKD1* and *PKD2* mutations (57). Based on previous studies of ADPKD mouse models with endothelial-specific *Pkd1* or *Pkd2* knockout, mutations in these genes impair cilia-mediated mechanosensation, leading to abnormal endothelial calcium signaling, defective flow-mediated vasodilation, and inflammation-associated endothelial dysfunction (108-110). This dysfunction may be particularly detrimental at cerebral arterial bifurcations, where disturbed flow and high hemodynamic stress make the vascular wall more likely to develop an aneurysm (111). Impaired endothelial mechanosensing may further disrupt endothelial-VSMC crosstalk, and dysregulated calcium signaling may promote the phenotypic switching and apoptosis of VSMCs, and activation of MMP (112). Thus, *PKD1* and *PKD2* mutations contribute to the formation of an IA indirectly by driving endothelial dysfunction, and directly by weakening the structural integrity of the vascular wall (113). An impaired vascular wall decreases vascular compliance and structural support (114). These mutations can also induce abnormal angiogenesis, which decreases vascular wall stability, impairs the blood supply and nutrient metabolism, and exacerbates damage of the vascular wall (6). Clinical studies have shown that specific *PKD1* and *PKD2* genotypes are associated with a greater risk of IA (14,110). In particular, patients with *PKD1* gene truncation mutations were found to have a significantly higher risk than those with other

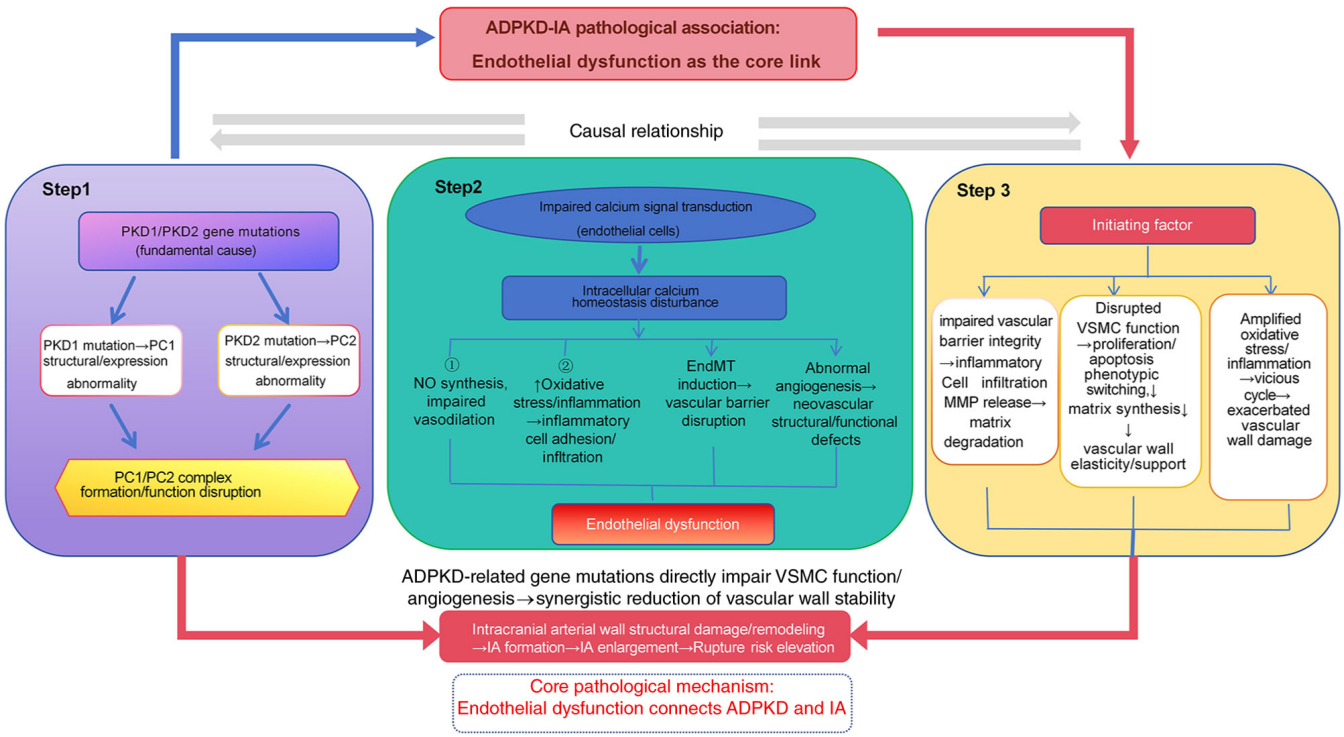

Figure 4. Endothelial dysfunction links ADPKD and IA. Mutations of *PKD1* and *PKD2* lead to a dysfunctional PC1/PC2 complex, impaired homeostasis of endothelial calcium, and endothelial dysfunction. Systemic endothelial dysfunction can damage the intracranial arterial wall and tissue remodeling. This can lead to the formation and enlargement of an IA, and increase the risk of IA rupture. ADPKD, autosomal dominant polycystic kidney disease; IA, intracranial aneurysm; *PKD1*, polycystic kidney disease 1; *PKD2*, polycystic kidney disease 2; PC1, polycystin 1; PC2, polycystin 2; NO, nitric oxide; EndMT, endothelial-to-mesenchymal transition; MMP, matrix metalloproteinase; VSMC, vascular smooth muscle cell.

mutations (14). These findings indicate that ciliary genetic defects and endothelial dysfunction both increase the risk of IA in patients with ADPKD because each has detrimental effects on vascular integrity and function (14).

5. Linking endothelial dysfunction, ADPKD, and IA

The aforementioned findings demonstrate that endothelial dysfunction is a core pathological link between ADPKD and IA. Specifically, ADPKD is characterized by a dysfunctional PC1/PC2 complex, and this disrupts calcium signaling and leads to endothelial dysfunction (14). This dysfunction can also initiate and increase damage of the intracranial arterial wall and remodeling, ultimately triggering an IA (Fig. 4) (88). This pathological process can be summarized as follows: i) ADPKD is caused by mutations of *PKD1* or *PKD2* (115). These mutations lead to structural alterations or abnormal expression of the PC1 and PC2 proteins and abnormalities or a deficit of the PC1/PC2 complex (116,117). Endothelial primary cilia are mechanosensory organelles that detect fluid shear stress, and normal PC1/PC2 signaling leads to flow-dependent endothelial responses (108). ii) Dysfunction of the PC1/PC2 complex directly impairs endothelial mechanosensation and flow-dependent calcium signal transduction (118). This disruption of calcium signaling induces endothelial dysfunction through multiple downstream pathways (73). Specifically, it manifests as decreased NO synthesis and impaired vasodilation (71), amplified oxidative stress and inflammation (119), and induction of EndMT, which compromises vascular barrier integrity and leads to pathological angiogenesis (120). iii) Building on these effects, endothelial dysfunction damages intracranial arterial walls and increases remodeling by decreasing the integrity of the vascular barrier, promoting the infiltration of inflammatory cells and the release of MMPs, and accelerating degradation of the ECM (121). Impaired endothelial sensing of blood-flow-induced shear stress can disrupt crosstalk between endothelial cells and VSMCs (122). This alters the function of VSMCs, leading to phenotypic transformation, decreased synthesis of the matrix, and an imbalance of cell proliferation and apoptosis. Collectively, these changes decrease vascular elasticity and structural support (123). Furthermore, endothelial dysfunction increases oxidative stress and inflammation, creating a self-perpetuating cascade that exacerbates vascular damage (124). The mutations responsible for ADPKD can also directly impair the function of VSMCs, further decreasing the function of vascular walls (125). Under the influence of blood flow pressure, the intracranial arterial wall can gradually bulge due to structural damage and decreased support, thus forming an IA (126). As vascular wall damage progresses, the size of an IA can increase, significantly elevating the risk of aneurysm rupture (127).

These pathological changes clearly demonstrate an association between ADPKD and IA (128). In particular, the gene defects in ADPKD induce endothelial dysfunction and link kidney disease to cerebrovascular complications. This provides a unified mechanistic framework for understanding the increased incidence of IA in patients with ADPKD (14). Oxidative stress and inflammation provide a link among

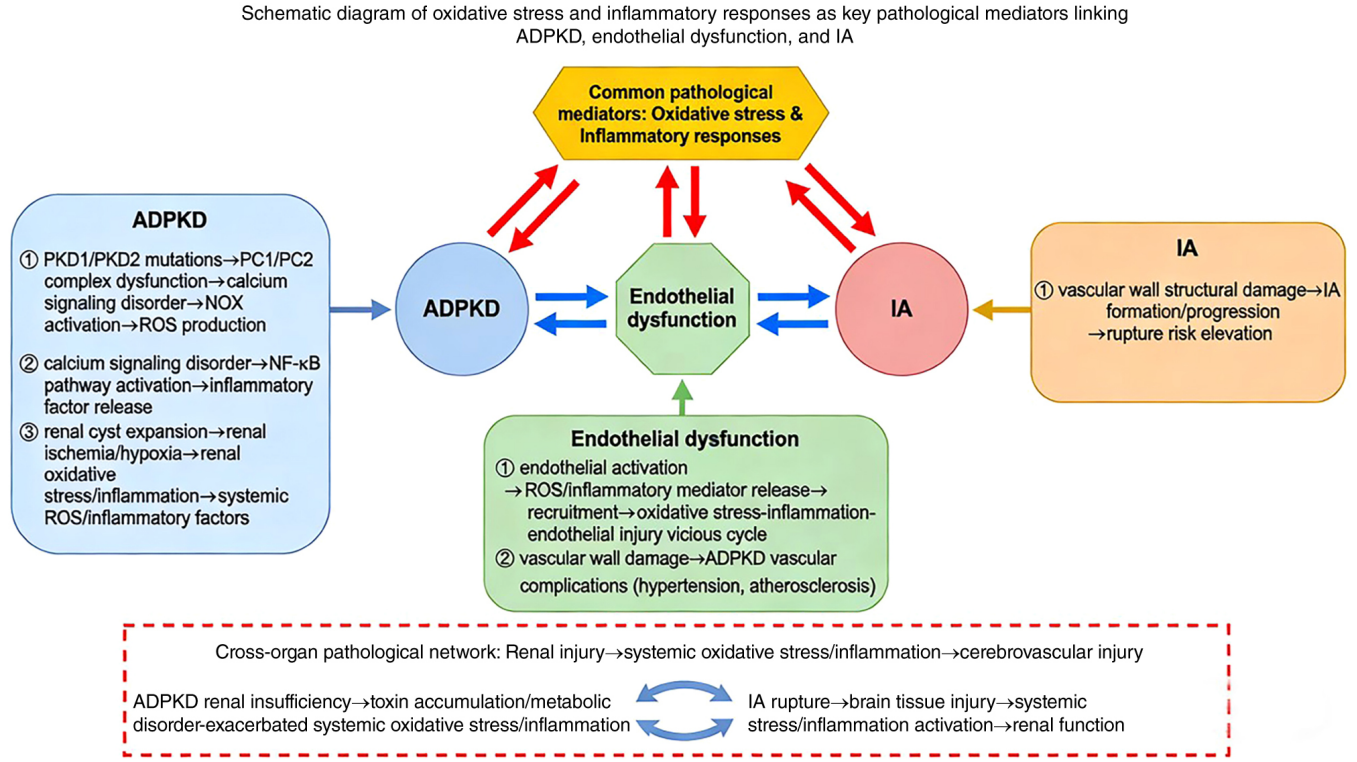

Figure 5. Bidirectional interactions between ADPKD, endothelial dysfunction, and IA are mediated by oxidative stress and inflammatory responses. ADPKD is initiated by mutations of *PKD1* or *PKD2* that disrupt formation of the PC1/PC2 complex. This leads to dysregulation of calcium signaling, and activation of NOX and NF-κB pathways, increased production of ROS and release of inflammatory factors, and renal hypoxia and ischemia. These systemic oxidative and inflammatory mediators trigger endothelial activation, creating a self-reinforcing cycle of endothelial injury that exacerbates vascular complications, such as hypertension and atherosclerosis. Endothelial dysfunction and damage of the vascular walls increases the risk for formation and progression of IA and IA rupture. IA rupture induces systemic stress and inflammation that further impairs renal function. The result is a multi-organ pathological network: renal injury → systemic oxidative stress and inflammation → cerebrovascular injury. ADPKD, autosomal dominant polycystic kidney disease; IA, intracranial aneurysm; *PKD1*, polycystic kidney disease 1; *PKD2*, polycystic kidney disease 2; PC1, polycystin 1; PC2, polycystin 2; NOX, NADPH oxidase; NF-κB, nuclear factor-κB; ROS, reactive oxygen species.

ADPKD, endothelial dysfunction, and IA (Fig. 5). The following section outlines this pathway as a sequential mechanistic framework.

First, ADPKD directly increases oxidative stress and inflammation (129). As aforementioned, mutations of *PKD1* and *PKD2* impair the mechanosensory PC1/PC2 complex, causing dysregulated calcium signaling and activation of NOX enzymes in endothelial cells (130). This promotes the production of ROS and triggers oxidative stress responses (131). Concurrently, dysregulated calcium signaling activates inflammatory signaling pathways, such as the NF-κB pathway, and this increases the release of pro-inflammatory factors (132). The formation of renal cysts and kidney enlargement in patients with ADPKD cause local ischemia and hypoxia, amplifying oxidative stress and inflammation in the kidney (133). The subsequent introduction of ROS and inflammatory factors into the systemic circulation causes oxidative damage and activates inflammatory pathways in endothelial cells throughout the body, including intracranial arteries, thus inducing systemic dysfunction of the endothelium (133).

Second, endothelial dysfunction accelerates the vascular complications attributable to ADPKD and the development of IA by amplifying systemic responses (134). Dysfunctional endothelial cells release excessive ROS and inflammatory mediators (135), allowing circulating inflammatory cells to infiltrate the vascular wall where they produce additional ROS and cytokines (136). This response is therefore a self-amplifying loop of oxidative stress, inflammation, and endothelial injury (137). This destructive cascade exacerbates endothelial dysfunction and also increases damage of vascular walls, and increases the risk for hypertension and atherosclerosis (138). Specifically the inflammation of intracranial arteries compromises their structural integrity, increasing the risk for the formation and progression of IA and IA rupture (139).

Third, oxidative stress and inflammation directly damage renal and intracranial arterial tissues, thus forming a cross-organ pathological network (140). Progressive enlargement of renal cysts leads to renal insufficiency, accumulation of uremic toxins, and metabolic disorders that further increase systemic inflammation and oxidative stress (141). These systemic factors continuously damage the intracranial arterial wall, induce endothelial dysfunction, and can promote development of an IA (142). Moreover, IA formation and rupture injure brain tissue, and this triggers a secondary systemic stress response and neurogenic inflammation (143). This bidirectional pathological feedback loop adversely affects renal function (144).

In summary, oxidative stress and inflammation are pathological mediators that are associated with ADPKD, endothelial dysfunction, and IA. Through inter-organ amplification, they form a complex pathological network that drives disease progression. Notably, identification of this pathological network allows identification of potential therapeutic targets (145).

6. Therapeutic implications and challenges

Given the central pathological role of endothelial dysfunction in ADPKD complicated by IA, therapeutic interventions that focus on restoring endothelial function may be promising (78). Specifically, the core objective of this strategy is to improve endothelial cell function by inhibiting oxidative stress and inflammation, and preventing vascular structural remodeling (146). These interventions aim to decrease the risk of AI in patients with ADPKD, delay the progression of existing IA, and prevent aneurysm rupture. These therapeutic strategies can be categorized as basic, targeted or innovative (147).

Basic intervention: Antioxidant and anti-Inflammatory therapies. Antioxidant and anti-inflammatory therapies have the potential to disrupt the destructive 'oxidative stress-inflammation-endothelial injury' cascade by decreasing the production of ROS and increasing the levels of antioxidants, thereby protecting endothelial function (135). NOX is a key target for antioxidant therapy, and selective and non-selective NOX inhibitors can decrease the generation of ROS and alleviate oxidative damage (148,149). Crucially, animal studies of ADPK models demonstrated that these inhibitors significantly improved endothelial function (150,151). Although exogenous antioxidants, such as vitamins C and E, can increase the antioxidant capacity of the body, their clinical efficacy requires validation (152). This anti-inflammatory therapy primarily consists of the alleviation of endothelial injury by inhibiting the NF-κB pathway or utilizing monoclonal antibodies against specific inflammatory factors (153). However, because systemic anti-inflammatory therapy can lead to profound immunosuppression, clinical applications require strict control of indications and dosages (154).

Targeted intervention: Drug development for ADPKD-related endothelial dysfunction. Targeted interventions address the specific genetic and functional defects of ADPKD-related endothelial dysfunction by focusing on restoration of flow-dependent vasodilation and correction of aberrant calcium signaling (126). Therapeutics that function as NO donors or eNOS activators can be considered as targeted interventions (155). NO donors directly increase the level of NO, and eNOS activators promote the endogenous production of NO. These agents therefore target defective upstream signaling pathways to improve vasodilation (156). Furthermore, agents that regulate calcium signaling can directly target the downstream consequences of abnormal PC1/PC2 complexes. Because *PKD1* and *PKD2* mutations impair the mechanosensory function of primary cilia, recent pharmacological research has also focused on specific channel activators and calmodulin modulators (157). These strategies may help compensate for defective ciliary mechanosensing, restore flow-responsive calcium-dependent endothelial signaling, and improve endothelial physiological function, thereby limiting pathological vascular remodeling and the development and progression of IA (158).

Innovative directions: Focusing on EndMT and vascular remodeling. Interventions that focus on EndMT and vascular remodeling aim to prevent damage of the vascular wall and to inhibit the TGF-β/Smad pathway (159). For example, TGF-β inhibitors can inhibit EndMT and improve endothelial function (160). In addition, agents that inhibit MMP activity and promote synthesis of the ECM have potential as interventions that enable therapeutic vascular remodeling (161). MMP inhibitors protect vascular integrity by decreasing degradation of the ECM; however, drugs promoting matrix synthesis require cautious use to avoid adverse effects, such as excessive cellular proliferation (162).

Assessing endothelial function for screening and personalized interventions. Endothelial dysfunction is the core pathological link between ADPKD and IA, and assessment of endothelial function can indicate the risk of IA in patients with ADPKD (14). Therefore, assessing markers of endothelial function in a regimen that screens for IA in patients with ADPKD has the potential to aid in the early identification of high-risk populations, diagnosis, and prognosis (163). Endothelial function can be assessed using three main types of markers or parameters: i) Vascular relaxation parameters, including two non-invasive procedures, flow-mediated dilation (FMD) and nitrate-mediated dilation (NMD) (164). FMD is an ultrasound technique that measures brachial artery dilation following reactive hyperemia, and the results indicate the extent of endothelium-dependent vascular relaxation. Thus, FMD directly assesses the mechanosensory and flow-dependent signaling capacity of endothelial cells *in vivo*. Because ADPKD-related polycystin dysfunction can impair flow-dependent endothelial mechanosensing (165), FMD values are typically lower in patients with ADPKD so these measurements could help to identify patients with a higher risk of IA (166). ii) Biochemical parameters, including NO and its metabolites, eNOS activity, ROS, inflammatory cytokines, adhesion molecules, and MMPs (167). These can be measured via blood tests or tissue biopsies, and provide a direct readout of endothelial function, oxidative stress, and inflammatory activation (168). Patients with ADPKD exhibit significantly decreased blood NO levels and markedly elevated levels of ROS, inflammatory factors, and MMPs, abnormalities that are closely associated with risk of IA (169). iii) Vascular permeability parameters: The integrity of the endothelial barrier can be assessed by dynamic contrast-enhanced magnetic resonance imaging or computed tomography (170). Due to endothelial dysfunction, the vascular permeability of intracranial arteries is significantly increased in patients with ADPKD; therefore, this parameter may serve as an important imaging biomarker for assessing the risk of IA (171).

Assessment of endothelial function-related indicators may help stratify IA risk in patients with ADPKD and support more personalized screening and intervention strategies (172). Thus, low-risk populations (those with normal endothelial biomarkers, no family history of IA, and no hypertension) can undergo IA screening every 5 to 10 years (173). Medium-risk populations (those with mildly abnormal markers of endothelial function, or hypertension, or a family history of IA) may require screening every 2 to 5 years and active control of hypertension and other risk factors (174). High-risk populations (those with highly abnormal markers of endothelial function, or with a high-risk PKD genotype, such as a *PKD1* truncating mutation) may require annual screening and comprehensive

interventions (175). The dynamic monitoring of endothelial function can also be used to evaluate the efficacy of different treatments and disease prognosis (176).

7. Clinical challenges and directions for future research

Although interventions that focus on restoring endothelial function provide new directions for the treatment of ADPKD complicated by IA, numerous clinical challenges must be addressed (177).

First, the application of multi-target synergistic therapies may be challenging due to the interconnected pathological pathways in ADPKD and IA (10). Each disease is characterized by multiple pathological cascades, defective primary cilia mechanosensation, aberrant calcium signaling, oxidative stress, and inflammation. This points to the need for development of effective multi-target treatment regimens (178). However, multi-target drug therapy may increase the risk of adverse drug effects (179). Optimizing drug combinations and dosages is an important challenge in translating a treatment regimen into clinical practice (180).

Second, there is an urgent need to address the safety and tolerability of long-term interventions (181). ADPKD is a chronic disease and IA development can occur over a prolonged period; thus, long-term interventions are required (10). However, the long-term safety and tolerability of potential therapeutic drugs have not yet been validated (182). Sustained use may lead to significant adverse effects, pointing to the need for strategies to mitigate safety problems in clinical applications (183).

Third, there are no personalized treatment plans based on ADPKD genotype (184). Patients with ADPKD exhibit significant genetic and phenotypic heterogeneity, and the pathological processes and treatment responses can differ in patients with different genotypes (185). The current lack of personalized treatment plans tailored to specific mutations limits treatment efficacy (186).

Fourth, the clinical translation of techniques for assessing endothelial function faces significant hurdles (187). Some methods are highly invasive or costly (188) and the results of non-invasive tests are easily influenced by factors such as patient status, environmental variables, and measurement techniques (188). There is a need to develop simple and accurate tests that reliably indicate the requirement for early intervention (189).

To address these challenges, it is suggested that future research should focus on the following topics: i) Conducting large studies to analyze the impact of different genotypes on endothelial dysfunction. Because ADPKD is associated with defective polycystin-dependent mechanosensing and impaired endothelial flow-mediated vasodilation, FMD appears to have potential as a clinically relevant indicator of dysfunctional vascular mechanotransduction (165,190). ii) Elucidating the structure and regulatory mechanisms of the PC1/PC2 complex may provide a rational basis for developing small-molecule therapeutics and gene-directed therapies that target these proteins. Interventions that restore polycystin-dependent signaling may help to correct flow-responsive calcium dysregulation and endothelial dysfunction, although their effects on the prevention of IA must also be considered (191,192). iii) Strengthening the development of non-invasive and sensitive techniques for assessing endothelial function, and validation of their application in patients with ADPKD in clinical studies (166). iv) Conducting large multicenter clinical trials to evaluate the efficacy and safety of various drugs in patients with ADPKD, and to identify the safest and most effective treatments for different patient populations (193).

8. Conclusion

The present review provides substantial evidence that endothelial dysfunction is a core pathological mechanism linking ADPKD and IA. Thus, *PKD1* and *PKD2* mutations in ADPKD are a fundamental cause of endothelial dysfunction. These mutations disrupt PC1/PC2-dependent endothelial mechanosensing, thereby inducing profound disturbances in flow-dependent intracellular calcium signaling. The subsequent decrease in NO synthesis, activation of oxidative stress and inflammation, and induction of EndMT contribute to severe endothelial dysfunction. Systemic endothelial dysfunction can also lead to the onset and progression of IA due to structural damage of the intracranial arterial walls and tissue remodeling, dysregulated VCMCs, and increased oxidative stress and inflammation. Additionally, mutations in *PKD1* and *PKD2* can directly disrupt angiogenesis, which, combined with endothelial dysfunction, further increases the risk of IA. Oxidative stress and inflammation increase systemic pathology in this complex network.

Based on these pathological mechanisms, interventions that aim to restore or repair endothelial function may be an effective new direction for the treatment of ADPKD complicated by IA. This approach can include application of basic antioxidant and anti-inflammatory agents, targeted approaches to improve endothelial relaxation and calcium signaling, and innovative strategies that focus on EndMT and vascular remodeling. The measurement of indicators of endothelial function during screening for IA risk in patients with ADPKD may enable the early identification of the most vulnerable patients and the application of individualized interventions. Regular monitoring of changes in endothelial function can also be used to assess the efficacy of different treatments and patient prognosis. However, the remaining challenges include the complexity of therapies that have multiple targets, the safety and tolerability of long-term interventions, the lack of individualized treatment plans, and difficulties in translating assessments of endothelial function into clinical practice.

Future research should examine the specific associations between different ADPKD genotypes and the nature and extent of endothelial dysfunction. This approach could begin by utilizing ADPKD rodent models to characterize specific vascular defects and to develop pharmacological agents that precisely target the PC1/PC2 complex and restore ciliary mechanosensation. Subsequent studies should aim to translate assessments of endothelial function by conducting multicenter, large-scale clinical trials to verify the efficacy and safety of potential therapeutics. The integration of basic research and clinical practice may enable the translation of mechanistic discoveries into clinical applications and provide novel strategies for the early screening and precise treatment of ADPKD complicated by IA. This could decrease the occurrence of IA and rupture-related mortality and improve patient quality of life.

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Authors' contributions

XX conceived and designed the review. XX and RX wrote, reviewed, and revised the manuscript. LZ performed literature searches. All authors read and approved the final manuscript. Data authentication is not applicable.

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Competing interests

The authors declare that they have no competing interests.

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