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It's Time for New Insights into Renovascular Hypertension at the Molecular Level

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Abstract

At the cellular level, reduced kidney perfusion in atherosclerotic renal arthery disease (ARVD), induces hypoxia, activation of the renin-angiotensin-aldosterone system (RAAS) and cytokine activation. Impaired blood flow in the kidneys creates a microenvironment triggering significant cytokine production, contributing to vascular damage and endothelial disfunction. Interactions between cytokines and endothelial, glomerular, and tubular cells often result in increased vessel permeability, and fibrosis, and contribute to the development of chronic kidney disease (CKD). Molecules such as endothelins, prostaglandins, and nitric oxide play a crucial role at the molecular level. The imbalance between vasoconstrictor and vasodilator factors contributes to vascular dysfunction. Oxidative stress and inflammatory processes at the cellular level contribute to endothelial damage and structural changes in blood vessels. Mineralocorticoid receptor antagonists (MRAs) therapy in the context of ARVD holds promise in reducing fibrosis, promoting angiogenesis and enhancing overall outcomes in patients with this pathology. Recent data also indicates the antioxidative, anti-inflammatory, and antifibrotic effects of SGLT2 inhibitors. They reduce oxidative stress caused by hypoxic conditions and enhance renal perfusion, contributing to the preservation of cellular function. Studies employing Blood Oxygen Level-Dependent (BOLD) imaging have identified adaptations to reduced blood flow, volume, and glomerular filtration rate in post-stenotic kidneys that preserve oxygenation in the medulla and cortex during medical therapy. Data from the literature indicate that despite the partial recovery of renal hypoxia and restoration of blood flow after revascularization, inflammatory cytokines and injury biomarkers remain elevated, and the glomerular filtration rate (GFR) does not recover in ARVD. Restoration of vascular patency alone has failed to reverse tubulointerstitial damage and partially explains the limited clinical benefit of renal stenting. Considering these findings, BOLD MR imaging emerges as a technique capa-

ble of providing insights into the critical juncture of irreversibility in ARVD. However, further research is needed to monitor renal hypoxia following renal artery stenting and the inflammatory response over an extended period in conjunction with optimal therapy involving MRAs and SGLT2 agonists. The aim of research at the molecular level enables the identification of potential therapeutic modalities targeting specific molecular pathways, opening the door to innovative approaches in treating renovascular hypertension.

Keywords

Renovascular Hypertension, Renal Hypoxia, Inflammatory Cytokines BOLD MR Imaging, New Therapeutic Modalities

1. Introduction

The association of atherosclerotic renovascular disease (ARVD) with chronic kidney disease (CKD) is well described; the kidney disease resulting from stenotic lesions in the renal arteries is termed ischaemic nephropathy [1].

The timely identification of patients who could benefit from endovascular stenting in ARVD, both in blood pressure control and the reduction of antihypertensive drug requirements, would illustrate a counterbalance to the findings of the CORAL and ASTRAL studies [2].

These studies manifest significant limitations, which have been the subject of various scientific discussions [3] [4].

In CORAL, for example, hypertension was not a requirement for entry, and ≈25% were at goal BP before enrollment [2].

The overall impact of these randomized trials on renovascular interventions has significantly diminished the perceived value of renal artery revascularization, restricting its use to extreme scenarios involving flash pulmonary edema or rapidly declining GFR.

We are at a time when standard antihypertensive drugs, including ACE inhibitors and angiotensin receptor blockers (ARBs), have been complemented by SGLT2 inhibitors, which also contribute to indirect blood pressure reduction [5] [6].

As we know, besides their use in the treatment of resistant hypertension for better regulation, MRAs (Mineralocorticoid Receptor Antagonists) are beneficial antifibrotic agents [7].

Timely and judicious selection of patients who will benefit from renal artery stenting should therefore be even more emphasized.

In that sense, it would be beneficial to take a look at what occurs at the cellular level in renal hypoxia, and it appears that BOLD imaging should be more frequently utilized for this purpose, especially to aid in selecting candidates for endovascular interventions in ARVD.

1.1. Epidemiology of ARVD

When considering the epidemiology of renovascular disease, it is important to note its classification into fibromuscular dysplasia (FMD) and atherosclerotic renovascular disease (ARVD).

Fibromuscular dysplasia (FMD) is an uncommon vascular condition that affects the entire circulatory system, with a higher incidence among younger women. It contributes to 10% to 20% of cases involving the narrowing of renal arteries. FMD is an idiopathic, non-inflammatory, non-atherosclerotic disease commonly involving renal and carotid arteries; however, it can affect any arterial bed [8].

ARVD is most common and is predominantly seen in older patients in the context of systemic atherosclerosis. Many of those plaques are extensions of aortic plaque into the renal artery. Hence, the location of atherosclerotic disease is usually near the origin of the artery, although it can be observed anywhere in the renal vessel. It can affect 1 or both renal arteries. Patients often have other associated risk factors, such as diabetes, hypertension, smoking history, peripheral vascular disease (PAD), coronary artery disease (CAD), chronic kidney disease (CKD) or abdominal aortic aneurysm (AAA) [9].

1.2. Pathophysiology of Renal Hypoxia

Currently it is widely accepted that ARVD with lumen stenosis > 70% will cause a reduction of renal blood flow and hypoperfusion of the juxtaglomerular apparatus, which in turn stimulates the release of renin followed by increased production of angiotensin II and aldosterone [9] [10] [11] [12] resulting in production of reactive oxygen species (ROS).

Patients with renovascular hypertension are ideal models for determining how endothelium-dependent vasodilation is affected by excess Ang II and an Ang II-related increase in oxidative stress [13].

An imbalance of nitric oxide (NO) and reactive oxygen species (ROS), so-called "oxidative stress," may promote endothelial dysfunction, leading to cardiovascular complications.

Endothelial dysfunction is the initial step in the pathogenesis of arteriosclerosis, resulting in cardiovascular complications [14], and independently associated with cardiovascular events [15].

The observation that all stages of atherosclerosis can occur at distant and multiple locations simultaneously, while sparing entire segments, may lead to the hypothesis that the interface and interaction between the vascular wall and circulation are the primary sites of the mechanism underlying cardiovascular events.

As early as 2005, Lerman [15] discussed endothelial injuries and the potential of bone marrow-derived endothelial progenitor cells (EPCs) to contribute to repair and play a role in tissue regeneration.

The concept of endothelial dysfunction should be extended beyond the conduit vessels into the vascular wall and even to the bone marrow and the proge-

nitor endothelial cells [15].

Studies investigating [16] the regulation of erythropoietin (EPO) production by the liver and kidneys, a classic physiological response to low oxygen levels, have led to the discovery of human oxygen-sensing mechanisms. These mechanisms are currently being targeted for therapeutic purposes.

This study aims to draw attention to potential revisions in guidelines for intervention, particularly emphasizing the need for a more nuanced approach in determining the efficacy of renal artery stenting in addressing inflammatory responses and preserving endothelial and renal function.

Considering these findings, Blood oxygenation level dependent (BOLD) MRI is an MRI contrast mechanism that depends on the oxygenation status of blood, specifically the oxygenation of blood hemoglobin (Hb) [17]. BOLD MR imaging emerges as a technique capable of providing insights into the critical juncture of irreversibility in specific renal pathologies. The method is completely non-invasive, since it utilizes an endogenous contrast mechanism and does not require injection of any exogenous contrast agent.

1.3. Adaptive Mechanisms as a Response to Renal Hypoxia

1.3.1. The Role of HIF (Hypoxia-Inducible Factor) in Renal Hypoxia

The pathophysiology of renal hypoxia involves various adaptive mechanisms activated in conditions of reduced blood flow and tissue hypoxia. Activation of hypoxia-inducible factor (HIF) and increased production of erythropoietin (EPO) are integral components of the adaptive response to renal hypoxia, aiming to compensate for the compromised blood flow and oxygen deficiency [18].

HIF (hypoxia-inducible factor) is a key regulator of the response to oxygen deficiency, and in the context of the kidneys, it plays a crucial role in regulating the production of erythropoietin EPO). When hypoxia occurs, during which time HIF accumulates and binds to specific sequences of the EPO gene, known as the hypoxia-responsive element (HRE) [19].

Activation of HIF in this manner promotes the transcription of the EPO gene, resulting in increased erythropoietin production. Therefore, HIF and erythropoietin are interrelated, where the activation of HIF due to hypoxia stimulates the production of erythropoietin to enhance red blood cell production and improve oxygen supply. This process plays a crucial role in the renal adaptation to hypoxia, promoting increased production of red blood cells to enhance oxygen supply [19].

However, prolonged or severe hypoxia can lead to pathological changes in the kidneys, including tissue damage and the development of chronic kidney disease.

Hypoxia is also a profibrogenic stimulus. Therefore studies utilizing HIF-stimulating agents proved efficacy in various kidney disease models, suggesting that HIF activation is an ideal target for future therapeutic approaches [18].

Recent researches demonstrate that HIFs play an important role in kidney injury and repair by regulating HIF target genes, including microRNAs. Any the-

rapeutic approach addressed at stabilizing HIF activity might have a potential benefit in ischemic nephropathy [20].

What's controversial is that in the early stages of disease or injury, HIFs may promote processes like tissue regeneration and protection. However, later on, excessive activation can contribute to pathology, including unregulated inflammation, fibrosis, uncontrolled cell proliferation, and oxidative stress.

In the context of renal hypoxia, HIFs stimulate the expression of genes leading to increased production of cytokines as inflammatory mediators of Tumor Necrosis Factor-alpha (TNF-α), Interleukin-1 (IL-1), Interleukin-6 (IL-6), Interleukin-8 (IL-8), Transforming Growth Factor-beta (TGF-β) [20].

In the initial stages, this inflammation can be adaptive; however, prolonged inflammatory responses contribute to progressive damage to renal tissue.

1.3.2. The Role of High Mobility Group Box 1 Protein (HMGB1) in Renal Hypoxia

Zhang *et al.* [21] demonstrated in an animal model that exposure to hypoxia causes molecular-level damage to renal tissue and activates the HMGB1-RAGE/TLR-TNF pathway.

High mobility group box 1 protein (HMGB1) serves as a proinflammatory agent and may have a central role in inflammation.

In conditions of tissue hypoxia, HMGB1 can migrate from the nucleus to the cytoplasm before being released into the extracellular space. Extracellular HMGB1 may promote inflammation by binding to receptors on effector cell membranes, including macrophages and dendritic cells and leads to the release of inflammatory mediators, including interleukin (IL)-6 and tumor necrosis factor (TNF)-α. In turn, the release of IL-6 and TNF-α leads to increased HMGB1 release, resulting in a cascade amplification of inflammation [21].

HMGB1 induces inflammation through binding to receptors for advanced glycation end products (RAGE) and Toll-like receptor (TLR), receptors through the nuclear factor kappa-light-chain-enhancer of active B cells (NF-κB) pathway [22].

The results of this study suggest that this pathway could be a key mechanism in kidney damage associated with obstructive sleep apnea and likely in hypoxia induced by ARVD which could be the subject of future research.

1.3.3. The Role of LTBP4 (Latent Transforming Growth Factor Beta Binding Protein 4) in Renal Hypoxia

LTBP4, or latent transforming growth factor beta binding protein 4, is a protein that plays a crucial role in regulating transforming growth factor beta (TGF-beta) activity. This protein is essential for processes such as fibrosis, inflammation, and angiogenesis in tissues, including the kidneys. Research suggests that a deficiency in LTBP4 is associated with the severity of acute kidney injury (AKI) [23] and the development of chronic kidney disease [24].

According to some studies, the absence of LTBP4 can significantly impact these renal conditions [24]. Extensive lines of evidence implicate TGFβ signalling in

lung fibrosis, neoplasm, cardiomyopathy, diabetic nephropathy (DMN), and inflammation, correlating with disease severity in all cases [25].

Therefore, understanding the mechanisms of TGFβ activation and its related signaling pathways is crucial in determining therapeutic strategies for cardiovascular diseases. This is particularly vital in the context of ARVD and prolonged hypoxia, where comprehending the role of LTBP4 may provide invaluable insights into the intricate pathophysiology and potential targets for intervention. TGFβ acts ubiquitously as a cytokine, playing a crucial role in the synthesis of extracellular matrix (ECM) molecules, contributing to fibrotic disorders and regulating the immune system [26].

Long-term hypoxia caused by renal artery stenosis has the potential to be a contributing factor to kidney fibrosis.

Renal fibrosis is characterized by the abnormal accumulation of ECM, with TGFβ1 as the central mediator, inducing increased matrix protein synthesis and inhibiting matrix degradation [27].

1.3.4. The Role of Vascular Endothelial Growth Factor B (VEGFB) in Renal Hypoxia

Vascular Endothelial Growth Factor B (VEGFB) and Vascular Endothelial Growth Factor A (VEGFA) are two distinct members of the vascular endothelial growth factor family that play a role in the regulation of angiogenesis.

In the study by Chi-Ting Sua *et al.* [24] it is described that LTBP4 affects renal fibrosis by influencing angiogenesis and altering mitochondrial structure. LTBP4 was found to stimulate vascular endothelial growth factor A (VEGFA) expression in hypoxic HK-2 cells but vascular endothelial growth factor B (VEGFB) expression was not significantly affected.

LTBP4 promoted VEGFB expression while, in hypoxia, LTBP4 enhanced VEGFA expression. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$; VEGF vascular endothelial growth factor, EGF epidermal growth factor, VEGFA vascular endothelial growth factor A, VEGFB vascular endothelial growth factor B, VEGFR1 vascular endothelial growth factor receptor 1, VEGFR2 vascular endothelial growth factor 2.

The results indicate that LTBP4 stimulates the expression of VEGFA but does not significantly affect the expression of VEGFB in hypoxic cells. The difference in their response to LTBP4 suggests that these factors may have specific roles in regulating the response to hypoxia [24].

In the context of renal artery stenosis and kidney hypoxia, LTBP4-induced angiogenesis may have a positive impact. The increased formation of new blood vessels could be a response to the oxygen deficiency (hypoxia) caused by renal artery stenosis, aiming to enhance blood supply and deliver nutrients to kidney tissues. Angiogenesis, in this case, might represent an adaptive response to preserve renal function under conditions of limited blood supply.

1.3.5. The Role of Mitohondrial Function and LTBP4 in Renal Hypoxia

Mitochondrial function is also associated with angiogenesis. Mitochondria are crucial for energy production in the form of ATP, and mitochondrial dysfunc-

tion can contribute to the development of hypoxia and kidney damage.

Chi-Ting Su *et al.* [24] also investigated the impact of the LTBP4 protein on mitochondrial function, particularly when cells are subjected to stress. In essence, the results suggest that LTBP4 positively influences mitochondrial function under stress conditions, potentially influencing processes such as angiogenesis and cellular energy production.

Results from the same study indicate that LTBP4 plays a crucial role in regulating the processes of mitochondrial fusion and fission. Reduced expression of mitofusin 2 (MFN2), a key mediator of mitochondrial fusion, in mice lacking the LTBP4 gene (Ltbp4S−/−) leads to exacerbated tubular damage and increased mitochondrial fragmentation.

In the context of fibrosis, this suggests that LTBP4 may have a protective role in preserving mitochondrial integrity, preventing further tubular damage, and reducing the risk of fibrosis development in the kidneys. These findings contribute significantly to understanding the molecular mechanisms linking LTBP4 to mitochondrial health and suggest potential therapeutic approaches to mitigate kidney damage and fibrosis development.

Research efforts should be directed toward identifying potential treatments that can aid in preserving mitochondrial function, reducing oxidative stress, and enhancing cellular energy performance. This could potentially mitigate kidney damage caused by renal vascular hypoxia.

1.3.6. The Role of Nitric Oxide (NO) in Renal Hypoxia

Nitric oxide (NO) plays a pivotal role in renal physiology, particularly in the context of hypoxia. NO, produced by endothelial cells, functions as a vasodilator, promoting blood vessel relaxation and improved blood flow. In conditions of renal hypoxia, the balance between NO and reactive oxygen species (ROS) becomes crucial.

Numerous reports have shown the influence of renin, NO and the endothelin (ET) systems for the regulation of blood pressure and renal function [28].

Hypoperfusion of the kidneys in ARVD acts as a stimulus for increased NO production by the endothelium. NO has a vasodilatory effect on the smooth muscles of the renal arteries, representing the body's attempt to compensate for reduced blood supply and ensure adequate oxygen and nutrient supply to renal cells.

In the model of 2K1C renovascular hypertension NO has been proven to be involved in maintaining blood flow. NO is thought to act as a vasodilatator and thereby antagonise the high levels of AT-II in both kidneys [29].

NO measurements have shown that endogenous NO production is increased in the contralateral kidney of 2K1C rats three weeks after clipping [30].

NO donors and NO-derived metabolites have been investigated in experimental renovascular hypertension and have shown promissory effects in attenuating blood pressure and organ damage in this condition.

Therefore, understanding the role of decreased NO in the pathophysiology of

renovascular hypertension promotes the study and development of NO donors and molecules that can be converted into NO (such as nitrate and nitrite), contributing to the treatment of this condition in the future [31].

1.3.7. The Role of Endothelin (ET) in Renal Hypoxia

The ETs comprise a group of three 21-amino acid peptides, having vasoactive, inotropic and mitogenic properties [32].

ET-1 acts on vascular muscle cells causing a long-lasting vasoconstriction [33]. Short-term renal artery stenosis in the 2K1C model of renovascular hypertension has resulted in an upregulation of renal ET1 in the clipped kidney.

Nitric oxide (NO) has been shown to down-regulate the expression of endothelin-1 (ET-1), while angiotensin II (AT-II) is recognized as a stimulator of ET-1 expression [34] [35].

Unfortunately, if hypoxia persists in ARVD, it leads to further damage to the endothelium and reduced NO secretion. This is another reason for emphasizing the importance of early recognition and treatment of ARVD.

It is generally accepted that the increase in renin secretion represents a neurohumoral counterregulation in the case of renal hypoperfusion to preserve renal perfusion after stenosis and maintain renal function.

Many previous studies have reported a decrease, but still elevated plasma renin levels in the chronic phase of renovascular hypertension [36] [37] [38].

as well as increased renin RNA levels in the clipped kidney and suppressed levels in the contralateral kidney in the early phase of 2K1C-hypertension [37] [38] [39].

Ritthaler *et al.* [40] demonstrated that short-term renal hypoperfusion has resulted in an upregulation of renal ET-1.

Research performed on patients after renal artery angioplasty has shown inconsistent results in changes in ET-1 levels.

While some studies did not observe changes in plasma ET-1 levels after repair, others reported an increase in ET-1 levels [41] [42].

Additionally, a study conducted on an animal model showed no difference in plasma ET-1 levels six weeks after experimental 2K1C-clipping compared to baseline [43].

Based on current knowledge, it has been indicated that research on hypoperfusion and the expression of endothelin genes in the context of atherosclerotic renovascular disease (ARVD) could provide additional insights into the mechanisms regulating endothelin. Considering the complex interactions between angiotensin II, the renin system, and endothelin, the question arises of how hypoperfusion and upregulation of the renin system may influence the expression of endothelins.

1.3.8. The Role of Blood NGAL (Neutrophil Gelatinase-Associated Lipocalin) in Renal Hypoxia

Blood NGAL ((neutrophil gelatinase-associated lipocalin) has been proposed as

a biomarker of renal ischemia, and it is a reliable and early biomarker of AKI [44] [45].

Eirin *et al.* [46] reported that NGAL levels are inversely correlated with eGFR in patients with ischemic nephropathy.

Cianci *et al.* [47] have recently published original data on NGAL and circulating renal stem cell (RSC) changes before and after PTRA and stenting in five patients with RAS.

They reported that the presence of high NGAL levels before revascularization is associated with lower RSC expression. However, an adaptative and reparative increase in the latter was also observed independent of baseline NGAL levels.

2. The Significance of Blood Oxygenation Level Dependent (BOLD) Imaging in Diagnosing Renal Hypoxia in Atherosclerotic Renovascular Disease (ARVD)

The functional assessment of renal tissue oxygenation in humans was possible only after the introduction of blood oxygen level-dependent magnetic resonance imaging (BOLD-MRI) [48].

This technique allows for the study of renal oxygenation status in relation to the degree of mild (G1), moderate (G2), and severe (G3) renal arthery stenosis (RAS). BOLD-MRI sensitivity and specificity in the identification of renal ischemia are related to the paramagnetic quality of deoxygenated hemoglobin, which modifies magnetic realignment after a field interruption, as opposed to to oxygenated hemoglobin, which has no active magnetic component [49] [50].

Blood oxygenation level-dependent magnetic resonance imaging (BOLD-MRI) is the most promising imaging technique to monitor renal tissue oxygenation in humans. BOLD-MRI measures renal tissue deoxyhaemoglobin levels voxel by voxel. Increases in its outcome measure R2* (transverse relaxation rate expressed as per second) correspond to higher deoxyhaemoglobin concentrations and suggest lower oxygenation, whereas decreases in R2* indicate higher oxygenation [49].

Most studies have not measured RBF, which complicates the interpretation of the results. In this respect, van der Bel *et al.* have shown that R2* values correlate strongly with the FF (GFR/effective renal plasma flow) in healthy volunteers, and they recommend performing simultaneous BOLD-MRI and phase contrast MRI to measure RBF in the renal artery [51].

This field was also hampered by the lack of prospective studies, but this changed since 1918 with the publication of Pruijm *et al.* [49] In their cohort of 112 CKD patients, 47 hypertensives and 24 healthy controls, CKD patients with high R2* values (>90th percentile) had a faster yearly estimated GFR decline and more often needed renal replacement therapy than those with lower R2* values [49]. This study strongly supports the hypoxia hypothesis and opens the door to more widespread implementation of renal BOLD-MRI in the clinical care for CKD patients.

Studies in human subjects with >60% obstruction of the renal artery have

enabled the determination of the haemodynamic significance of the stenosis. Interestingly, cortical and medullary R2* values were preserved in many patients with moderate obstructions of the renal artery, despite a fall in stenotic kidney RBF and GFR by 30% - 35% [52].

It seems that the presence of moderate obstruction of the renal artery does not necessarily lead to a significant decrease in R2* values in the cortex and medullary regions of the kidney. This suggests that, although there may be a reduction in blood flow and glomerular filtration rate in the stenotic kidney, the tissue can maintain a certain level of oxygenation. This could be crucial for understanding the relationship between renal artery obstruction and tissue hypoxia and any potential clinical consequences.

However, kidneys distal to severe luminal obstructions showed more pronounced hypoxia [52] with increased tissue injury, interstitial fibrosis and inflammation [53].The degree of renal hypoxia by BOLD-MRI in those stenotic kidneys correlated directly with the severity of fall in single-kidney RBF and serum injury biomarkers in the draining renal vein [54] [55].

In essence, severe renal artery stenosis can induce significant renal hypoxia leading to tissue injury and/or a complete lack of response to furosemide, indicating minimal residual blood flow to the kidney. BOLD-MRI may contribute to the clinical assessment of renal artery stenosis, but further research is necessary for meaningful clinical advancements [50].

3. Therapeutic Perspectives at the Molecular Level in ARVD

3.1. The Role of Mesenchymal and Resident Stem Cells in Renal Inflamation and Repair

Mesenchymal stem cells (MSCs) are fibroblast-like stromal cells that have been isolated first from the bone marrow and successively from several other organs and tissues, including the kidney [56] [57] [58]. Many recent studies have focused on the exploration of their therapeutic potential in different renal damage conditions. MSCs ability to migrate and/or differentiate in the kidney following several renal insulting mechanisms defines the extraordinary repairing potentiality of these peculiar cells. Once migrated or activated in the damaged kidney, MSCs produce and release, through extracellular vesicles and exosomes, a variety of cytokines and chemokines able to reduce inflammation and increase different reparative pathways [47] [58]. Some reports in animal models have explored the potential restorative role of stem cells after renal reperfusion and have demonstrated encouraging and promising results [59] [60]. One of these emerged in the preclinical studies conducted by Textor's group [61]. Renal microcirculation reparation, inflammatory damage attenuation, and renal function restoration were the observed effects of MSC infusion. The positive effects of stem cells are mediated by paracrine effects associated with the release of soluble mediators and extracellular vesicles, as well as pericyte activation [58]. Podocytes and tubular cell progenitors have been found in the Bowman's capsule. Both cell ty-

pologies show a heterogeneous ability to differentiate and regenerate after renal ischemia/reperfusion [61] [62]. Cianci *et al.* [47] previously reported the first human case of successful post-reperfusion renal recovery accompanied by a significant increase in circulating RSCs in a revascularized patient with bilateral RAS. In different interesting studies conducted on animals by the Fan Yang group and others, fat-derived MSCs showed a marked reparative, anti-inflammatory, and anti-fibrotic ability in streptozotocin-induced diabetic nephropathy [63] [64] [65]. The interest on MSCs has rapidly increased in recent years. Their preliminary use with a renal regenerative, anti-inflammatory, and anti-fibrotic aim in several studies conducted on cell cultures, animals, and humans has shown promising translational results [47] [56] [57] [58].

3.2. The Role of Endothelium in Renal Inflammation and Repair

Many studies have demonstrated that abnormal lipid metabolism, inflammatory responses, and hemodynamic alterations are critical players in the occurrence of endothelial dysfunction and Atherosclerosis [66].

A reduction in endothelium-derived NO is one cause of endothelial phenotypical alterations presenting as impaired endothelium-dependent vasodilation. Once activated, endothelial cells express various adhesion molecules, such as ICAM-1, MCP-1, VCAM-1, P-selectin, and E-selectin, which attract neutrophils and monocytes that attach to the activated endothelial cells and penetrate the arterial wall [67].

The monocytes will then differentiate into macrophages within the vessel wall and engulf Oxidized LDL (oxLDL) to become foam cells, which are a histopathological hallmark of atherosclerosis. Exposure of endothelial cells to various stimuli causes oxidative stress and further amplifies the vicious cycle of vascular inflammation and atherosclerosis [68].

Oxidized LDL (oxLDL) induces endothelial cell injury via impairing cholesterol efflux, increased apoptosis signal-regulated kinase 1/NLRP3 inflammasome signaling, and endoplasmic reticulum stress [69].

In light of the important role of oxidative stress in endothelial dysfunction, detecting novel markers (e.g., oxidatively modified lipids and proteins) of oxidative stress and applying antioxidants may represent a promising strategy for the prevention of endothelial dysfunction-associated diseases.

In the past two decades, several clinical trials and meta-analyses have been conducted to evaluate the beneficial effects of antioxidants such as vitamin C, vitamin E, xanthine oxidase inhibitors, α-lipoic acid, and the synthetic agent NXY-059 [70] [71] [72] [73]. However, the protective effects were not observed in large clinical trials. Recent years have witnessed the development of Nrf2 activators

[74] [75], NADPH oxidase inhibitors [76] [77], and the ROS scavenger mitoQ [78] as promising novel antioxidant approaches. In addition, the poly (ADP-ribose) polymerase inhibitor PJ-34 ameliorates cerebromicrovascular endothelial func-

tion and improves cognitive performance in aged mice by decreasing oxidative stress [79].

3.2.1. Inhibition of Endothelium Inflammation as a Novel Therapeutic Strategy

Vascular inflammation plays an important role in the initiation and progression of atherosclerosis and other forms of CVD [80]. In response to injury, endothelial cells become activated and produce interleukin (IL)-8, chemokines, colony-stimulating factors, interferons, monocyte chemoattractant protein-1 (MCP-1), intercellular adhesion molecule-1 (ICAM-1), P-selectin, E-selectin, vascular adhesion molecule-1 (VCAM-1), growth factors, and other inflammatory factors. These substances attract monocytes and neutrophils, which attach to the activated endothelium, penetrate the arterial wall, and initiate inflammation [81]. Proinflammatory mediators such as TNF-α and IL-1β stimulate endothelial cells to secrete other proinflammatory cytokines, including IL-6, that stimulate liver cells to produce and release diverse acute-phase reactants, including fibrinogen and c-reactive protein, that modulate both chronic inflammation and the acute-phase response [82]. However, the anti-inflammatory cytokines IL-35 and IL-10 block endothelial activation via reducing mitochondrial ROS production [83].

Inhibition of endothelium inflammation has emerged as a novel therapeutic strategy to reverse endothelial dysfunction.

Recent studies have also revealed that TFEB, a Kruppel-like factor 2 (KLF2)-dependent target formed under laminar flow, exerts anti-inflammatory effects in diabetic mice by suppressing IκB kinase (IKK) activity [84].

Activation of KLF2 and Kruppel-like factor 4 (KLF4) (master regulators of vascular homeostasis) inhibits inflammation in endothelial cells in response to proinflammatory cytokines [85] [86].

Sun *et al.* reported in 2019 that the activation of G protein-coupled receptor 81 inhibits endothelial inflammation by reversing oscillatory shear stress-induced KLF2 downregulation and upregulating the expression of MCP-1 and VCAM-1 [87]. Pharmacological activation of KLF2 by lipid-lowering statins modulates endothelial function [85] and prevents atherosclerosis by upregulating several of its downstream transcriptional targets [88].

Aloperine (an alkaloid) prevents endothelial inflammation, leukocyte adhesion to activated endothelial cells, and atherogenesis via the activation of atheroprotective transcriptional factor KLF2 through suppression of the phosphorylation of p53 protein [89].

3.2.2. Sodium-Glucose Cotransporter 2 Inhibitors and Endothelial Protection

Canagliflozin, dapagliflozin and empagliflozin are the most well studied SGLT2i with cardiovascular actions. Canagliflozin (30 mg/kg, oral gavage,8 weeks) was recently reported to prevent endothelial dysfunction by improving endothelium-dependent relaxation, which reduces vascular oxidative stress and inflam-

mation. These beneficial effects eventually translate into reduced atherogenesis in diabetic apolipoprotein E knockout (ApoE−/−) mice [90]. This study extends the obsevation from a previous study showing that canagliflozin reduced plaque size and increased plaque stability in ApoE −/− mice by reducing vascular inflammmation [91].

Similar antiatherosclerotic effects of dapagliflozin have been observed in a rabbit model of atherosclerosis [92] and in a mouse model of diabetic atherosclerosis [93]. Clinical data from the DEFENSE study reveal that dapagliflozin improves endothelial function and glycemic control in patients with T2DM [94]. Mechanistic studies identified that dapagliflozin reduced endothelial activation and increased endothelium-dependent relaxation [95].

The cardiovascular protective actions of empagliflozin have been observed in the EMPA-REG outcome trial [96]. The possible mechanisms of benefit include increased NO production and endothelium-dependent vasodilation, reduced vascular inflammation and oxidative stress, restored structural integrity of the glycocalyx, attenuated endothelial cell senescence, and antiatherosclerotic effects [97] [98].

4. Conclusions

To date, only a few studies have examined hypoxia-related inflammation biomarkers and their changes after percutaneous transluminal renal angioplasty (PTRA) with and without stenting. A more well-explored focus is on the effects of different reno-protective drugs on pro-inflammatory and pro-fibrotic molecular pathways in chronic renal ischemia; however, we still see an increase worldwide in patients with atherosclerotic ischemic nephropathy that initiate dialysis.

Our research strongly supports the pivotal role of endovascular reperfusion as the gold standard in treating renal artery stenosis, emphasizing the critical importance of timely intervention and preserved circulation below the stenosis.

In addition to renoprotective drugs and kidney revascularization, new insights into renal damage pathways in hypoxia due to ARVD should also encompass stem cell regeneration, mitochondrial protection, and angiogenic cytokine therapy.

We highlight recommended therapeutic options, including anti-RAAS medications, SGLT2 inhibitors, and anti-endothelin agents, for patients ineligible for endovascular reperfusion. Furthermore, we propose the expanded use of biomarkers such as TGF-β, MCP-1, VEGF, and NGAL, alongside BOLD-MRI, in clinical practice to enhance pre and post-revascularization diagnostics and monitoring.

The role of oxidative stress in endothelial dysfunction and ARVD has been well recognized.

Nitric oxide (NO) plays a pivotal role in renal physiology, particularly in the context of hypoxia. NO, produced by endothelial cells, functions as a vasodila-

tor, promoting blood vessel relaxation and improved blood flow. In conditions of renal hypoxia, the balance between NO and reactive oxygen species (ROS) becomes crucial.

Numerous reports have shown the influence of renin, NO and the endothelin (ET) systems for the regulation of blood pressure and renal function

Hypoperfusion of the kidneys in ARVD acts as a stimulus for increased NO production by the endothelium. NO has a vasodilatory effect on the smooth muscles of the renal arteries, representing the body's attempt to compensate for reduced blood supply and ensure adequate oxygen and nutrient supply to renal cells.

The role of oxidative stress in endothelial dysfunction and ARVD has been well recognized. Further exploration of novel therapeutic targets in regulating exaggerated ROS generation and mitigating existing oxidative stress and the accompanying ARVD is essential for designing novel antioxidant therapies. The optimal timing of the window of administration of antioxidants at different stages of ARVD is another important consideration. Therapeutic agents that inhibit NF-κB, YAP/TAZ, and TLR4, and those that activate KLF2/KLF4 and TFEB, hold great potential in treating endothelial dysfunction and CVD. The discovery of novel transcription factors that regulate endothelial inflammation is an active area of investigation. Further identification of novel drugs or repurposed drugs targeting inflammation-associated transcription factors is warranted.

BOLD-MRI provides a wealth of information in patients with severe vascular disease, although the interpretation of the results is difficult, and combination with measures of renal blood flow, glomerular filtration rate (GFR) or tissue injury will clearly increase its usefulness.

BOLD-MRI is also a powerful tool to gain insight into the renal effects of drugs, thanks to the ability to repeat the exam as often as needed without side effects or ionizing radiation burden. In this regard, BOLD-MRI is of interest to pharmaceutical companies, since it has the potential to identify possible nephrotoxic or nephroprotective properties of drugs at an early stage.

It is crucial to note that only a limited number of studies have longitudinally assessed endothelial injury markers in combination with BOLD imaging post-stenting, comparing this to a control group receiving only optimal medical therapy. Further translational research studies that combine all hypoxic statuses, inflammation degrees, fibrotic pathways, and roles of MSCs in renal regeneration would be essential for a more accurate selection of patients with ischemic nephropathy eligible for revascularization. Emphasizing the perspective of MSC infusion as a potentially revolutionary therapy for patients developing renal fibrosis due to ARVD-induced ischemia and hypoxia underscores the importance of continued research in this domain.

Once migrated or activated in the damaged kidney, MSCs produce and release, through extracellular vesicles and exosomes, a variety of cytokines and chemokines able to reduce inflammation and increase different reparative path-

ways. Paracrine and/or endocrine mechanisms are involved, with effects on both immune response modulation and cellular replacement. It has been reported, that MSCs express several cytokine and chemokine receptors that may be functional during migration to the sites of inflammation.

Timely and effective treatment MSCs infusion, used alone or combined with PTRA and reno-protective drugs, could represent an additional future innovative treatment for patients with any form of renal ischemia.

Our findings not only contribute to the advancement of scientific understanding but also emphasize the practical implications for clinical practice, encouraging sustained efforts in improving care for ARVD patients.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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