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Study Perspective

Mesenchymal Stem Cells Infusion and Renal Revascularization in Atherosclerotic Renal Artery Stenosis - New Modalities in Therapeutic Approach

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Abstract

Recent studies indicate increased Renal Blood Flow (RBF) and cortical perfusion after Mesenchymal Stem Cells (MSCs) infusion in Atherosclerotic Renovascular Disease (ARVD) patients.They underscores the importance of exploring the new therapeutic modalities alongside endovascular stenting. Delivery of MSCs into the stenotic kidney at the time of revascularization preserves oxygen-dependent tubular function and microvascular architecture, and decreases inflammation and fibrosis. Recovery of cortical perfusion and eGFR has been observed in the contralateral kidney according to recent studies.

MSC therapy plays a crucial role in promoting cell proliferation and migration, enhancing angiogenesis while inhibiting apoptosis and inflammation. Furthermore, they preserve endothelial function and provide protection against the progression of fibrosis. To emphasize the potential of MSCs in treating ARVD patients, the aim of this study is to highlight the need for a longer follow-up period. Continuing with a larger patient sample and an extended follow-up period of over 6 months, future research should explore the efficacy of MSCs in restoring endothelial function and microvascular rarefarction in ARVD after stenting. Additionally, there is a need to evaluate treatment guidelines for these patients, which were based on studies conducted almost a decade ago, such as CORAL and ASTRAL.

Introduction

Atherosclerotic Renovascular Disease (ARVD) is the most common cause of secondary hypertension and is predominantly seen in older patients in the context of systemic atherosclerosis. Hence, the location of atherosclerotic disease is usually near the origin of the renal artery and can affect one or both renal arteries [1]. 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) [2].

While moderate Renal Artery Stenosis (RAS) may be asymptomatic, hypertension eventually develops as RAS progresses. A commonly used criterion to identify hemodynamically significant stenosis is a decrease of at least 60% of the luminal diameter of the renal artery, which is associated with a peak systolic velocity > 200–300 cm/s per Doppler ultrasonography [1,2]. Nonetheless, studies have shown that the stenotic kidney is able to adapt to moderate flow reduction allowing relatively safe long-term use of antihypertensive drug therapy to control blood pressure [3].Over time, some renovascular occlusions progress and medical therapy alone fails to treat refractory hypertension.

Two large clinical trials, ASTRAL and CORAL, demonstrated that renal revascularization had no advantage when compared to the medical treatment and does not improve outcomes in ARVD. This might because not merely chronic hypoxia and reduced blood flow, but activation of the Renin Angiotensin Aldosteron Sistem (RAAS), increased oxidative stress and cytokine release, microvascular dysfunction and rarefaction, and kidney fibrosis are involved in the underlying mechanisms [4].

Recent studies have shown that, alongside hemodynamic factors, inflammation and endothelial injury are the most significant contributors to ARVD progression.

Fortunately, there are evolutionary mechanisms involved in endothelial defense against hypoxia. Yanmeng Yang [5] et al., have concluded that a hypoxic environment can positively influence different functions (proliferation, survival, homing, differentiation, and paracrine activities) of MSCs.

Abumoawad et al. [6] observed increased cortical and whole kidney blood flows in the post-stenotic kidney of subjects with ARVD over a three-month period following intra-arterial infusion of autologous adipose-derived MSC.

MSC therapy play a crucial role in promoting cell proliferation and migration, enhancing angiogenesis while inhibiting apoptosis and inflammation.

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

Molecules such as endothelins, prostaglandins, and nitric oxide play a crucial role at the molecular level [7].

An imbalance of nitric oxide (NO) and reactive oxygen species (ROS), so-called “oxidative stress,” may promote endothelial dysfunction, leading to cardiovascular complications. [8].

Impaired blood flow in the kidneys triggers significant cytokine production, contributing to vascular damage. Interactions between cytokines and endothelial, glomerular, and tubular cells often result in increased vessel permeability, fibrosis, and contribute to the development of chronic kidney disease (CKD) [9].

The New Therapeutic Perspectives in Renal Hypoperfusion

Not all ARVD patients are suitable for endovascular intervention, especially due to advanced age and comorbidities. For others, an early diagnosis and timely renal artery stenting with optimal drug therapy could potentially bring more benefits. Therefore, selecting the right candidates for renal artery stenting and introducing new medications that contribute to preserving endothelial integrity are crucial for future research and guidelines.

The role of Sodium-Glucose Co-Transporter-2 (SGLT-2) inhibitors in CKD and Renal Hypoperfusion

Cardiovascular outcome trials with Sodium-Glucose Co-Transporter-2 (SGLT-2) inhibitors in patients with type 2 Diabetes Mellitus (DM) suggested that these agents can effectively delay the progression of CKD in these individuals. (10).The Study-to-Evaluate-the-Effect- of-Dapagliflozin-on-Renal-Outcomes-and-Cardiovascular- Mortality-in-Patients-With-Chronic-Kidney-Disease (DAPA-CKD) is a recent milestone in the field, as it included patients with both diabetic and non-diabetic proteinuric CKD and showed impressive reduction in the primary renal outcome of CKD progression, as well as the risk of hospitalization for heart failure and all-cause mortality on top of standard- of-care treatment [10]. Based on the above, relevant guidelines should accommodate their recommendations to implement treatment with SGLT-2 inhibitors for CKD patients with ARVH and renal hypoperfusion. Due to the well-known physiological mechanism of action and increased excretion of sodium and glucose, they may have an indirect antihypertensive effect.

The role of MRAs in CKD,Endothelial Dysfunction and Renal Hypoperfusion

Aldosterone is thought to play a role in the development of hypertension, vascular structure alteration, endothelial dysfunction, left ventricular remodelling, collagen synthesis, renal and myocardial fibrosis [11].

Mineralocorticoid receptor antagonists (MRA) are essential in the treatment of chronic kidney disease (CKD) due to their anti-

inflammatory and antifibrotic effects [12,13]. The first invented MRA was spironolactone, which has nonselective actions and affects androgen and progesterone receptors [13]. Nowadays there are also two other groups of MRA available, the more selective eplerenone [12,13] and the novel, nonsteroidal, selective MRA—finerenone, esaxerenone, apararenone [14]. Among all MRA, nonsteroidal new-generation MRA appear to have better anti-inflammatory and antifibrotic effects; moreover, they cause minimal hyperkalemia and a lesser decrease in the estimated glomerular filtration rate (eGFR) during therapy [14].

Recent studies have evaluated the effects of classical steroidal MRA (spironolactone, canrenone, and eplerenone), as well as new nonsteroidal MRA such as finerenone and esaxerenone, [14-17]. The results showed that in the group of patients with stage two and three CKD and a high plasma aldosterone concentration, the use of MRA may be effective in preventing the progression of CKD [16,17].

If we refer to these new findings, we can conclude that MRA may have a positive impact on arterial hypertension and slowing the progression of CKD in ARVD patients.

The role of Mesenchymal Stem Cells in Renal Hypoperfusion

As the reduction in Renal Blood Flow (RBF) increases, the transition from a purely hemodynamic phase to an inflammatory one begins, since the reduction in renal oxygenation will activate the proinflammatory and fibrotic pathways, which could be reversed if renal ischemia is promptly treated [18,19].

In agreement with relevant studies, inflammation plays a key role in the transition from Acute Kidney Injury (AKI) to CKD in ischemic nephropathy [19,20].

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 [17]. Many recent studies have focused on the exploration of their therapeutic potential in different renal damage conditions. [17,21].

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. Paracrine and/or endocrine mechanisms are involved, with effects on both immune response modulation and cellular replacement [15,18].

The secretion of paracrine factors committed to inhibiting the release of interleukin-1α (IL-1α) and tumor necrosis factor α (TNF-α) and to increasing the secretion of the IL-1 receptor antagonist are reported mechanisms explaining the ability of differentiated MSCs to repair injured kidneys [15,19].

Moreover, it has been reported that differentiated MSCs are also able to influence the activity of macrophages by enhancing their pivotal role in cell replacement and repair through the reduction of inflammation, the clearing of apoptotic cells and debris, and the promotion of tissue remodeling and regeneration [20]. Macrophage activation and function depend on the inflammatory stimuli received by the damaged tissue microenvironment. As the repair process progresses from the initial inflammatory phase to the remodeling phase, macrophages successively exhibit variable polarization and activation states [21,22].

Textor et al. [23] demonstrated in their study increase in cortical and whole kidney blood flows in the post-stenotic kidney for subjects with ARVD over a three month period after intra-arterial infusion of autologous adipose-derived MSC. These changes were associated with partial reduction of renal vein inflammatory and angiogenic biomarkers and dose-related changes in GFR and blood pressure. No such changes were observed in a medically-treated group, for whom blood flows and GFR were stable or tended to decrease over the same interval. The change in RBF associated with MSC infusion for the post-stenotic kidney resulted from increased cortical and medullary perfusion as no measurable changes in kidney volumes were identified. By contrast, the medical treatment only group had no change or a decrease in RBF in the post-stenotic kidney over the course of three months. Levels of tissue hypoxia within stenotic kidneys measured by BOLD MR fell in MSC treated subjects [23].

The role of BOLD-MR in Renal Hypoperfusion

Development of blood oxygen level–dependent (BOLD) MRI methods can allow functional evaluation of regional differences in deoxyhemoglobin levels within the kidney without requiring contrast [23]. Studies with BOLD imaging have identified adaptation to substantial reductions in renal blood flow, volume, and glomerular filtration rate in post-stenotic kidneys that preserves medullary and cortical oxygenation during medical therapy. However, extreme vascular compromise overwhelms these adaptive changes and leads to cortical hypoxia and microvascular injury [24].Saad et al. [25] demonstrated in their study that fractional tissue hypoxia, rather than cortical or medullary R2* values used to assess renal BOLD MR imaging, exhibits a direct relationship with chronically reduced blood flow and glomerular filtration rate (GFR). We believe that the BOLD MR method should be more widely utilized in practice, especially in AVRD patients.

Conclusion

Studying renal ischemia in all its variations (renal artery stenosis, renal artery stenosis with nephrosclerosis, and atherosclerotic renal vascular disease), it is known that the damaged tubule undergoes repair over a period of 8-12 weeks, likely mediated by specialized cells previously classified as survivor epithelial cells. These cells, expressed close to the damaged renal tissue, correspond to renal survivor cells (RSCs).

They are believed to be renally committed MSCs that migrate and differentiate into RSCs at the site of tissue damage in response to various stimuli. MSCs express several cytokine and chemokine receptors that may function during migration to inflammatory sites. Moreover, it has been reported that during ischemia, hypoxia-inducible factor 1 alpha (HIF-1α) can protect MSCs against oxygen-glucose deprivation-induced injury by inducing autophagy and activating the intracellular PI3K/AKT/mTOR signaling cascade. Under hypoxic conditions, the expression of stromal cell-derived factor 1 (SDF-1) has been found to increase within the kidney. The identification of SDF-1 receptor (CXCR4) expression on MSCs further demonstrates the chemotactic activity induced by hypoxia on MSCs with a protective and reparative goal. Pre-incubation of MSCs with TNF- α has been shown to enhance MSC migratory capacity, indicating that the SDF-1/CXCR4 interaction may mediate the localization of exogenously injected MSCs to hypoxically damaged renal tissue with potential therapeutic effects.

Research on renal ischemia highlights the importance of MSCs as key players in the process of repairing damaged tubules, opening the door to innovative therapeutic approaches. The future of treatment may lie in nanoengineering, where MSCs could be programmed to precisely target damaged tissue and promote its regeneration. This revolutionary therapy could not only change the way we treat renal ischemia but could also mark the beginning of a new era in medicine.

However, it is important to emphasize the need for a randomized study with a longer follow-up period after the application of stem cells and stenting, not just the three months that previous studies have lasted. This would provide more robust evidence regarding the efficacy and safety of these interventions, guiding future clinical practice. Additionally, inclusion of patients with ARVD and chronic kidney disease who are also receiving SGLT2 inhibitors and MRAs alongside conventional RAAS blockade in potential studies is crucial, as these drugs have shown endothelial protection through studies. The mechanisms preserving the integrity of MSCs and addressing their migration to damaged tissue increase the hope for future successful use of these cells in the treatment of renal ischemia, even in the case of extensive intrarenal vascular-bed compromise and fibrosis onset. Therefore, we urge the scientific community to explore these possibilities with enthusiasm and openness, as we stand on the brink of a potentially transformative period in the treatment of this complex condition.

Author Contributions

Conceptualization, LJ.F.D; writing-original draft preparation, LJ.F.D,; writing-review and editing, B.V. and T.G.; visualization, supervision, B.V. ,M.G. and LJ.F.D.; All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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