Does the Greater Omentum ("Policeman of the Abdomen") Possess Therapeutic Utility in CKD?

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CKD is a progressive disorder that results in ESRD, requiring chronic hemodialysis or a kidney transplant, and affects 400 million individuals globally and 36 million individuals in the United States. In up to 50% of all cases, CKD is caused by diabetic nephropathy (DN). CKD per se and its associated and progressive cardiovascular comorbidities constitute a major health burden for affected patients as well as a financial burden for the health care system. Because of the magnitude of this medical problem, intensive efforts into the elucidation of underlying pathomechanisms are ongoing worldwide. A large number of potential therapeutic targets have been identified, most of which have shown some promise, primarily in preclinical studies and less so in clinical applications. Common morphologic features of most forms of CKD include progressive glomerulosclerosis and tubulointerstitial fibrosis with tubular atrophy, microvascular rarefaction, and the appearance of myofibroblasts that deposit excess extracellular matrix. Oxidant stress and related inflammation are well recognized profibrotic mediator mechanisms that are currently the primary focus of preclinical and clinical work that tests various drugs that are designed to reduce renal fibrosis via inhibition of these mechanisms. US Food and Drug Administration–approved drugs to slow the progression of CKD to ESRD, particularly when proteinuria is present, currently include renin-angiotensin-aldosterone system inhibitors (e.g., spironolactone) and non-dihydropyridine calcium channel blockers.

The renal damage seen in CKD of other etiologies is also present in DN, but it is compounded by more pronounced lesions in the tubulointerstitium and blood vessels. Modestly effective therapies in patients with diabetes who are at risk for or diagnosed with DN include glycemic and BP control, smoking cessation, weight loss, and renin-angiotensin-aldosterone system inhibition once albuminuria and CKD have developed.

Bardoxolone methyl, which acts as an antioxidant and an anti-inflammatory agent that downregulates NF-κB signaling via induction of the NF erythroid 2–related factor, recently failed in a phase III clinical trial in patients with stage 4 CKD caused by DN. This negative outcome was in large part due to study drug–induced serious adverse events, such as congestive heart failure, weight loss, hypertension, and death.

A potential explanation regarding the relative ineffectiveness of current drug-based therapies in CKD may be the fact that most drugs target only a single or a few of its complex pathomechanisms. Although such agents may be ameliorating one pathophysiologic component of CKD, they may “ignore” others, and some drugs have been found to cause adverse effects, as was the case with bardoxolone methyl.

Given the number of pathogenic pathways that contribute to the development and progression of CKD, and the likely compounding effects of comorbidities, an ideal therapy would simultaneously or successively target all major pathomechanisms. Such therapy is currently not available. This potential limitation in the effectiveness of drugs in CKD resembles, in part, what was observed when preclinically effective drug therapies (e.g., atrial natriuretic peptide, IGF-1, and erythropoietin) obtained in otherwise healthy animals with AKI failed in clinical trials of study participants that had significant comorbidities. Of note, we observed that the successful treatment of AKI with mesenchymal stem cells—cells that possess potent paracrine/endocrine anti-inflammatory, antiapoptotic, antifibrotic, angiogenic, and mitogenic activities—prevented subsequent development of CKD both in animals and in study participants in our phase I clinical trial in patients who had on-pump cardiac surgery.

In a number of recent preclinical studies, we and others demonstrated that the administration of mesenchymal stem cells to rats with experimental CKD, induced by 5/6 nephrectomy, improved outcomes, as evidenced by the stabilization or improvement of renal function as well as the reduction in proteinuria, glomerulosclerosis, and interstitial fibrosis. Similar responses were obtained with the administration of bone marrow–derived endothelial precursor cells.

Tengion, Inc. has treated five CKD patients to date with its “Neo-Kidney Augment” product in Sweden, a cell-based therapy that has been well tolerated thus far, although preliminary efficacy data are not yet available. This therapy utilizes isolated autologous tubular cells obtained by a biopsy of the diseased kidney. A subgroup of tubular cells is culture expanded and injected together with biodegradable material into the
diseased kidney. This cell-based therapy has shown beneficial effects in rats with 5/6 nephrectomy–induced CKD, as well as in rats with DN and in dogs with a reduction of kidney mass. It is expected that this therapy results in similar delays in the clinical development of ESRD.

In this issue of JASN, Garcia-Gomez and colleagues describe the therapeutic efficacy of an omentum-mediated cell or stem cell therapy in rats with 5/6 nephrectomy–induced CKD. This beneficial therapy is elicited by the spontaneous attachment of the “activated” omentum to the cut surfaces of the remnant left kidney. At 12 weeks after 5/6 nephrectomy and 13 weeks after activation of the omentum, serum creatinine and BUN levels as well as the degrees of glomerulosclerosis and interstitial fibrosis were significantly improved compared with controls with CKD (omentectomy patients and animals without prior activation of the omentum). However, proteinuria was not decreased. This work is based on previous observations by the authors in which they demonstrated that the intraperitoneal administration of polydextran particles (approximately 120 μm in diameter) results in the activation of the rodent omentum, because of the rapid accumulation and retention of these inert particles. The activated status of the omentum is characterized by increased numbers of stem cell–like or progenitor cells, located primarily around the incorporated dextran particles and in perivascular areas that are expanded as a result of increased angiogenesis. In addition, this particle-induced activation of the omentum resulted in the increased expression of vascular endothelial growth factor by stromal cells as well as cells that express stromal cell–derived factor 1, C-X-C motif chemokine receptor 4, and Wilms’ tumor 1, markers of adult progenitor cells. In addition, increased numbers of cells expressing Oct-4, Nanog, and stage-specific embryonic antigen 1 were detected, identifying an embryonic-type stem cell population. The kidney tissue injured by prior resection and to which the activated omentum fused contained large numbers of proliferating cells, improved vascularity and perfusion, increased levels of proangiogenic, and repair-supporting vascular endothelial growth factor and IGF-1 as well as cells expressing genes, such as Sca-1, Wilms’ tumor 1, and CD34, which are respective markers of stem cells or progenitor cells. It is thought that the latter are delivered by the attached omentum exerting the beneficial intrarenal actions of this intervention in the 5/6 nephrectomy model of CKD, likely through paracrine mechanisms. Singh et al. previously showed that the dextran particle–activated omentum fused with the rodent liver that was injured by wedge resection, resulting in repair and growth of the rodent liver.

The greater omentum consists of a thin double layer of mesothelial cells that is attached to the greater gastric curvature. It folds back on itself and returns to the transverse colon and reaches beyond to the posterior peritoneum. In addition to its fat cells, the greater omentum is well vascularized and contains omentum–associated lymphoid tissue, historically called “milky spots.” These milky spots contain mostly macrophages as well as B, T, mast, and stromal cells that are closely associated with capillary loops that resemble those seen in renal glomeruli. Both the vascular endothelium and the overlying mesothelial cell layer of the milky spots possess gaps that permit the exit into the peritoneum of bloodborne cells as well as the entry into the omentum of cells and particulate matter from the peritoneum. Inflammatory stimuli caused by peritonitis, injuries, or particulate matter cause a reversible expansion of these milky spots, a response that is essential to the omentum’s ability to fight infections and carry out tissue repair. This ability prompted the British surgeon Morison to call the omentum the “policeman of the abdomen” in 1908. Significantly, surgeons, for many years, have utilized these beneficial characteristics of the omentum to improve the healing of wounds, fistulas, and anastomoses, and to favorably affect neurologic, cardiac, pelvic, musculoskeletal, intrathoracic, and other remote pathologic processes.

Overall, the data reported by Garcia-Gomez et al. are novel and scientifically interesting, confirming the ability of this unique omentum-mediated therapy to slow 5/6 nephrectomy–induced CKD that specifically results from the acute insult that bilateral resection of the kidney imparts on the remnant kidney. In other words, these data confirm earlier observations that stem cell therapy of experimental ischemia reperfusion–induced AKI prevents the subsequent development of CKD. There are, however, obvious limitations to the applicability of this technology to clinical CKD, because the activated omentum only attaches to the sites where kidney tissue has been acutely resected and thus appears to generate undefined recruitment signals to the mobile omentum. In addition, 5/6 nephrectomy disrupts the posterior peritoneum and thereby facilitates the access of the omentum to the retroperitoneally located kidney. Whether this beneficial omental interaction occurs later in the course of 5/6 nephrectomy–induced CKD or in other models of CKD (e.g., DN or ligation of select renal artery branches) has not been tested. There are also no published reports on the spontaneous omental attachment to the kidney in patients with progressive CKD. For this effect to be clinically beneficial in patients with chronic CKD, it would be necessary for the greater omentum to spontaneously enter into the retroperitoneal space and to attach itself to the diseased kidney, which is unlikely to occur. However, the capacity of the omentum to stimulate the repair of a kidney that has undergone an acute resection for the removal of a tumor or other lesion, and to potentially delay the secondary development of CKD, could be feasible. Although the authors clearly demonstrate that an omentum that has not been activated lacks its organ-protective activities in experimental CKD, there is a substantial body of literature that has demonstrated the clinical efficacy of the normal omentum in the treatment of many intra- and extra-abdominal conditions. Finally, further studies are needed to fully define the complex nature of the omentum’s ability to heal injured organs and to establish its potential utility in patients with renal diseases.
REFERENCES


