Shaping Tomorrow's Nephrology: Insight-Driven Kidney Care
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Emerging Anti-Inflammatory and Novel Pathway-Targeted Therapies

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Diabetic kidney disease (DKD) remains the leading cause of chronic kidney disease and kidney failure worldwide despite substantial therapeutic advances over the past decade. The introduction of renin–angiotensin system inhibitors, sodium-glucose cotransporter-2 (SGLT2) inhibitors, nonsteroidal mineralocorticoid receptor antagonists, and glucagon-like peptide-1 receptor agonists has significantly improved renal and cardiovascular outcomes. However, many patients continue to experience progressive kidney function decline despite optimized standard-of-care treatment. This persistent risk, often referred to as residual inflammatory burden, has shifted attention toward inflammation, oxidative stress, immune activation, and fibrosis as major contributors to DKD progression. Multiple inflammatory pathways have been implicated in DKD pathogenesis. Among the most extensively studied are the MCP-1/CCR2 axis, JAK-STAT signaling, IL-6-mediated inflammation, NLRP3 inflammasome activation, oxidative stress pathways, and complement activation. These pathways promote macrophage recruitment, cytokine production, endothelial dysfunction, podocyte injury, tubular damage, and extracellular matrix accumulation, ultimately leading to progressive fibrosis and loss of kidney function. Biomarkers such as TNF receptor-1 and -2, MCP-1, IL-6, and complement activation products have consistently been associated with accelerated DKD progression and adverse renal outcomes. Several targeted therapies have entered clinical development during the past two decades. CCR2 antagonists such as CCX140-B and MCP-1 inhibitors demonstrated reductions in albuminuria in phase 2 studies, supporting the therapeutic potential of suppressing monocyte-mediated inflammation. Similarly, the JAK1/2 inhibitor baricitinib reduced albuminuria and inflammatory biomarkers in patients with DKD, providing proof-of-concept for cytokine pathway inhibition. More recently, oxidative stress has emerged as an attractive therapeutic target. The pan-NADPH oxidase inhibitor APX-115 demonstrated

favorable albuminuria-lowering effects and a good safety profile in a randomized phase 2a study, highlighting the potential of directly targeting reactive oxygen species generation upstream of inflammation and fibrosis. Although no anti-inflammatory therapy has yet achieved the transformative impact observed with SGLT2 inhibitors in DKD, ongoing phase 2 and phase 3 studies continue to explore novel anti-inflammatory, anti-fibrotic, and complement-targeted approaches. Future progress will likely depend on biomarker-guided patient selection and precision medicine strategies that identify inflammatory, complement-driven, or fibrotic phenotypes most likely to benefit from targeted intervention. Such approaches may represent the next major step toward reducing residual risk and improving long-term renal outcomes in patients with diabetic kidney disease.

Keywords: diabetic kidney disease, inflammation, oxidative stress, anti-fibrotic therapy, targetd therapy