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The role of advanced glycation end products and RAGE in diabetic nephropathy: Pathophysiological mechanisms and therapeutic implications

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Abstract

Diabetic nephropathy (DN) is one of the most severe microvascular complications of diabetes mellitus and a leading cause of chronic kidney disease and end-stage renal failure worldwide. Persistent hyperglycemia triggers a network of pathogenic mechanisms, including increased formation of advanced glycation end products (AGEs), activation of the receptor for AGEs (RAGE), oxidative stress, chronic inflammation, and profibrotic signaling. AGEs accumulate in long-lived proteins and renal tissues under sustained hyperglycemia, and their interaction with RAGE activates multiple intracellular pathways that amplify oxidative damage, inflammatory mediator release, extracellular matrix deposition, and podocyte injury. The AGE/RAGE axis plays a central role in the development of glomerular hyperfiltration, albuminuria, mesangial expansion, basement membrane thickening, and progressive glomerulosclerosis. Furthermore, the phenomenon of metabolic memory indicates that early hyperglycemic exposure can induce long-term renal damage even after glycemic improvement. This review summarizes current insights into the molecular mechanisms linking AGE and RAGE to DN and highlights potential therapeutic strategies targeting this pathogenic pathway.

Keywords: Diabetic nephropathy, Advanced glycation end products, RAGE, Hyperglycemia, Oxidative stress, Renal fibrosis, Metabolic memory

Introduction

Diabetic nephropathy (DN) develops as a major complication of both type 1 and type 2 diabetes mellitus and is a predominant cause of chronic kidney disease and end-stage renal disease globally (1, 2). Diabetic nephropathy are the leading cause of end-stage kidney disease in the United States and most developed countries. Diabetes accounts for 30% to 50% of the incident cases of end-stage kidney disease in the United States. Although this represents a significant public health concern, it is important to note that only 30% to 40% of patients with diabetes develop diabetic nephropathy (3).

Clinically, DN manifests with albuminuria, reduced glomerular filtration rate (GFR), hypertension, glomerulosclerosis, and tubulointerstitial fibrosis (3). Chronic hyperglycemia constitutes the main driving factor for cellular injury, activating several intertwined pathways such as the polyol pathway, protein kinase C (PKC) activation, oxidative stress, and the formation of AGEs (4). Among these mechanisms, the AGE/RAGE axis is particularly significant because it translates persistent metabolic disturbance into chronic inflammation and fibrosis (5). The kidney, a key organ in glucose homeostasis, becomes functionally overwhelmed in diabetes, leading to metabolic overload and progressive structural deterioration [6]. Genetic predispositions, hypertension, and obesity can accelerate this process, while early glycemic control remains the most effective protective measure (6).

Methods

This article is a narrative review of the literature on the role of advanced glycation end products (AGEs) and their receptor (RAGE) in diabetic nephropathy. Relevant studies were identified through searches in major scientific databases using keywords including “AGE”, “RAGE”, “diabetic nephropathy”, “oxidative stress”, “inflammation”, and “fibrosis”. Peer-reviewed articles published in English and relevant to the topic were selected and reviewed to summarize current knowledge on molecular mechanisms and potential therapeutic strategies.

Hyperglycemia and cellular injury

Chronic hyperglycemia induces biochemical and structural perturbations across multiple renal cell types [7]. Fasting hyperglycemia is a hallmark feature of diabetes that results from impaired glucose homeostasis and insulin resistance (7). The normal process of glucose metabolism in the body when blood glucose levels are normal. Under aerobic conditions, most glucose is metabolized to pyruvate through glycolysis. Pyruvate is then oxidized to acetyl-CoA, which enters the tricarboxylic acid cycle. Ultimately, glucose is oxidized to water and carbon dioxide, producing energy for the body. However, in a high glucose environment, the glycolysis process can become saturated, meaning that most glucose cannot complete normal metabolism. This stimulates the collateral metabolism pathways, such as the polyol and sorbitol pathways. Excessive activity in these collateral pathways can lead to metabolic imbalances and biochemical disorders in key tissues, including the kidneys. These imbalances can result in irreversible changes in function and even structure of the tissues (8).

Glucose overload initiates excessive flux through collateral metabolic routes, generating toxic intermediates and oxidative stress (9). Podocytes—specialized cells forming part of the glomerular filtration barrier —are highly vulnerable to hyperglycemia, and their injury results in proteinuria and progressive glomerular destruction (10). In early disease, glomerular hyperfiltration occurs, causing mechanical strain and capillary damage, particularly under concomitant hypertension (11). Hyperglycemia also triggers mitochondrial dysfunction and inflammation, leading to apoptosis and renal fibrosis. Cellular injury accumulates over years, culminating in irreversible loss of nephrons and kidney function (12, 13) (Figure 1).

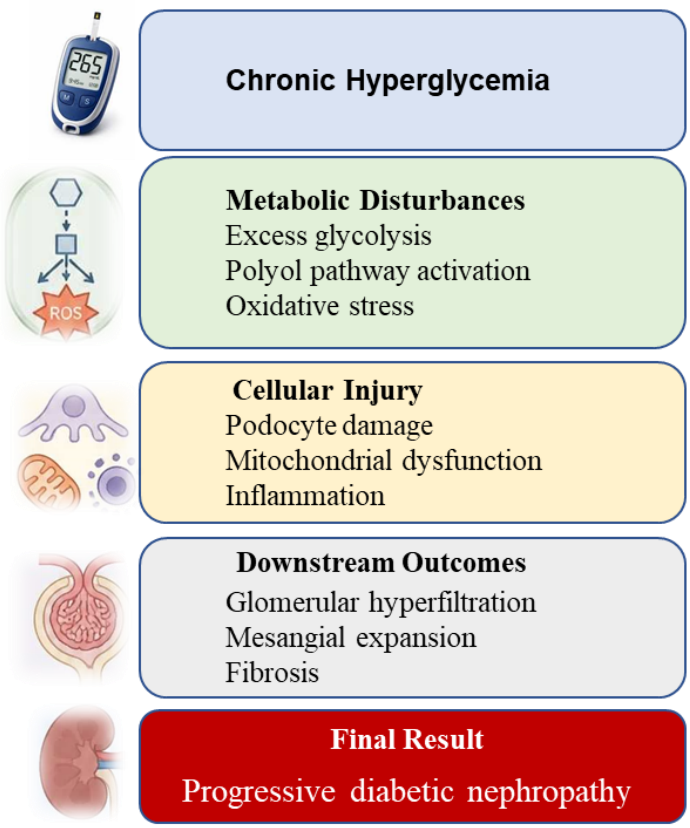

Figure 1. Chronic hyperglycemia induces metabolic disturbances and cellular injury, leading to glomerular dysfunction, fibrosis, and ultimately progressive diabetic nephropathy.

The receptor for advanced glycation end (RAGE)

RAGE is a multiligand transmembrane receptor belonging to the immunoglobulin superfamily (14). Besides AGEs, RAGE binds HMGB1 and S100/calgranulin, enabling broad activation of inflammatory signaling (15). A soluble isoform, sRAGE, functions as a decoy receptor that neutralizes circulating AGEs, hence reducing membrane-bound RAGE activation. Decreased levels of sRAGE correlate with increased vulnerability to diabetic complications (16). In experimental models, RAGE inhibition ameliorated renal inflammation, apoptosis, and fibrosis (17).

The binding of the ligands to RAGE has two effects: (1) it stabilizes the formation of oligomers, which are complexes made up of multiple RAGE molecules, and (2) it facilitates cell signaling. The oligomers are important for transmitting signals across the cell membrane and for amplifying the signal strength. The ligand-bound RAGE oligomers then interact with intracellular signaling proteins, which trigger a cascade of events that regulate various cellular processes such as cellular migration, proliferation, and adhesion. These processes are essential for maintaining tissue structure and function, and for responding to changes in the environment such as injury or infection. Therefore, the binding of ligands to RAGE plays an important role in regulating cellular processes and maintaining tissue homeostasis (18).

Rage signaling pathways

Binding of AGEs to RAGE activates intracellular pathways mediated by Rho GTPases, MAPKs (JNK, p38, ERK), NF-κB, and AP-1 transcription factors (6). NF-κB activation is a hallmark of RAGE signaling, driving transcription of cytokines and adhesion molecules and further amplifying RAGE expression, forming a vicious self-perpetuating

cycle (19). RAGE signaling upregulates transforming growth factor-β (TGF-β) and enhances fibrosis through extracellular matrix accumulation (20). MyD88-dependent signaling links RAGE activation to innate immune pathways, while ROS generation from NADPH oxidases intensifies redox imbalance (Figure 2). These mechanisms synergistically promote renal cell apoptosis, podocyte damage, and loss of filtration capacity (21, 22).

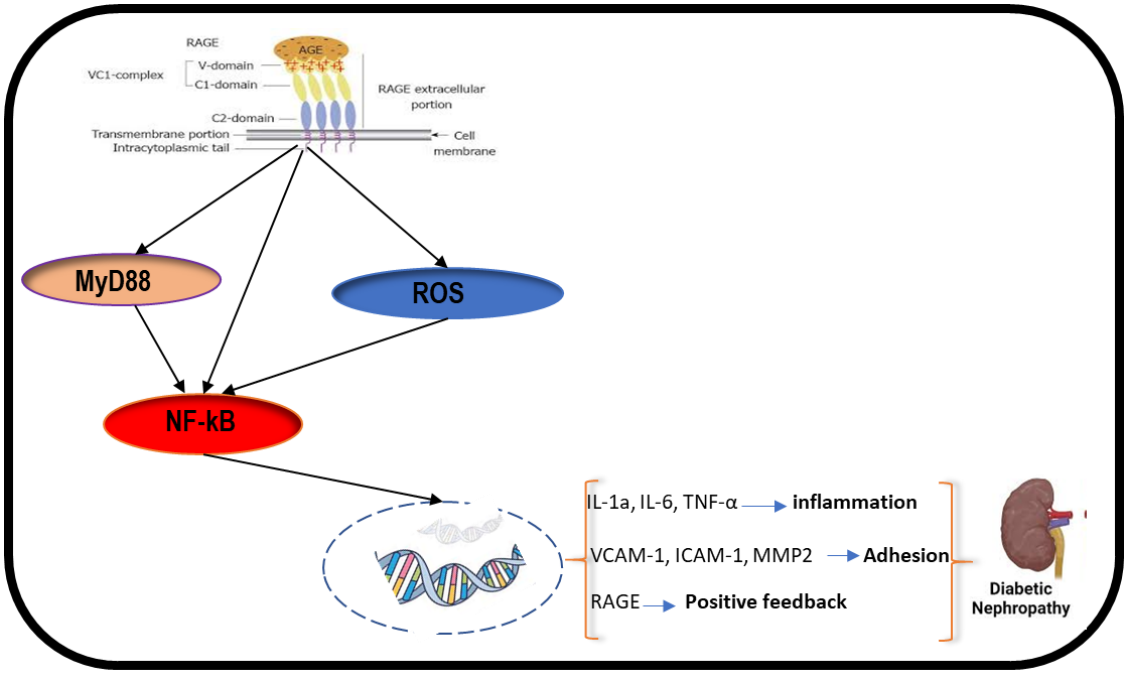

Figure 2. Intracellular RAGE signaling.

Rage and diabetic kidney disease

In the diabetic milieu of the kidneys, AGEs are highly abundant and can upregulate the expression of RAGE (23). When RAGE is activated by AGEs, it leads to the generation of reactive oxygen species (ROS) and amplifies inflammation in the kidneys. This chronic inflammatory state can cause a gradual loss of kidney architecture and function over time (24).

Furthermore, RAGE activation by AGEs can also result in the up-regulation of enzymes such as nicotinamide adenine dinucleotide phosphate oxidase (NADPH oxidase), nitric oxide synthase (NOS), and cyclooxygenase (COX), which can exacerbate and intensify inflammation (25). AGE-mediated RAGE activation has also been shown to create endoplasmic reticulum (ER) stress and elevate intracellular calcium levels. These events can lead to increased apoptosis rates, or programmed cell death, in cultured murine podocytes (26).

Additionally, RAGE activation on glomerular podocytes can promote the secretion of Heparanase, an enzyme that degrades heparin sulfate, which is an integral part of the glomerular basement membrane (GBM). The degradation of heparin sulfate by Heparanase can disintegrate the filtration barrier of the GBM, which can lead to the leakage of proteins and other substances into the urine (27).

Furthermore, mice that overexpress RAGE develop more severe forms of nephropathy after the induction of diabetes (28)and conversely, RAGE-deficient diabetic mice demonstrate delayed development of diabetic kidney disease, express less inflammatory and fibrotic mediators in renal tissues, and become more resistant

against renal cell apoptosis compared to wild-type animals(29) This implies that RAGE activation may play a role in the progression of diabetic nephropathy, and that therapies targeting RAGE activation may be helpful in slowing or preventing the development of this condition.

Metabolic memory

The term "metabolic memory" describes the lasting impact of advanced glycation end-products (AGEs) that have accumulated in the body (30). These AGEs can continue to cause over-expression of a receptor called RAGE, sustained activation of a protein called NFκB, and inflammation in specific tissues even after blood glucose levels have been lowered (31-33). This can lead to long-term oxidative stress, which is associated with the development and progression of complications related to diabetes (34, 35). These complications, which affect both large and small blood vessels in the body, can significantly reduce quality of life and increase the risk of morbidity, disability, and death. They also contribute significantly to healthcare costs (36, 37).

Therapeutic strategies targeting AGE/RAGE signaling

AGE-Lowering Approaches

Therapeutic interventions aim to reduce AGE burden by inhibiting their formation, enhancing detoxification, decreasing dietary AGE intake, or administering antiglycation agents. Antioxidant therapy indirectly limits glycoxidation by mitigating oxidative stress (38).

RAGE Inhibition

Pharmacologic modulation through RAGE antagonists, neutralizing antibodies, soluble decoy receptors (sRAGE), or downstream signaling inhibitors has shown renoprotective effects in experimental settings [20]. Such therapies attenuate inflammation, oxidative stress, and fibrotic remodeling, providing strong rationale for future clinical trials (39).

Conclusion

Diabetic nephropathy (DN) is a multifactorial disorder that develops through complex interactions among metabolic, hemodynamic, inflammatory, and fibrotic pathways that progressively impair renal structure and function. Chronic hyperglycemia promotes several pathogenic mechanisms, among which the advanced glycation end product–receptor for AGE (AGE–RAGE) axis has emerged as a pivotal mediator linking metabolic disturbance to renal injury (40).

Persistent accumulation of AGEs in diabetic tissues leads to sustained activation of RAGE on renal cells including podocytes, mesangial cells, endothelial cells, and tubular epithelial cells. Engagement of RAGE triggers multiple downstream signaling pathways that enhance the production of reactive oxygen species (ROS), largely through activation of NADPH oxidase, and promotes the activation of transcription factors such as nuclear factor-κB (NF-κB) (40, 41). Activation of these pathways results in increased expression of pro-inflammatory and pro-fibrotic mediators including transforming growth factor-β (TGF-β), connective tissue growth factor (CTGF), monocyte chemoattractant protein-1 (MCP-1), and intercellular adhesion molecule-1 (ICAM-1), which collectively contribute to glomerular injury, extracellular matrix accumulation, podocyte dysfunction, and progressive renal fibrosis (40).

In addition to promoting inflammation and oxidative stress, AGE–RAGE signaling is strongly implicated in the phenomenon of metabolic memory, whereby prior periods of poor glycemic control continue to exert deleterious effects even after glucose levels are normalized. This persistent cellular dysfunction is thought to involve epigenetic modifications, mitochondrial damage, and sustained activation of inflammatory signaling pathways that perpetuate renal injury over time (42, 43). Experimental studies further support the central role of RAGE in DN pathogenesis, as animal models overexpressing RAGE exhibit accelerated renal injury, whereas RAGE

deficiency or pharmacologic blockade significantly attenuates albuminuria, inflammation, and structural kidney damage (44, 45).

Taken together, these findings highlight the AGE–RAGE axis as a key pathogenic driver of diabetic nephropathy. Therefore, therapeutic strategies aimed at reducing AGE formation, enhancing AGE detoxification, inhibiting RAGE expression, or blocking downstream signaling pathways may represent promising approaches for slowing or preventing the progression of diabetic kidney disease. Such strategies, when combined with strict glycemic control, may help interrupt the vicious cycle of oxidative stress, inflammation, and fibrosis that ultimately leads to renal failure in patients with diabetes.

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