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Review

The Influence of Hyperglycemia on Renin-Angiotensin System Activation in Diabetic Nephropathy

Mohammed Ibrahim Alsubhi[1*], Saad Munawwikh Alshammari[2], Omar Mebrek Almutairi[2], Abdulaziz Mohammed Alshammari[3], Ali Mohammed Abu Tuwaymah[2], Rayan Hamad Alsedrani[2], Saleh Mohammed Almeteb[2]

[1] *Department of Family Medicine, National Guard Hospital, Jeddah, Saudi Arabia*
[2] *Hail Health Cluster, King Khalid Hospital, Hail, Saudi Arabia*
[3] *Department of Family Medicine, Ministry of Defense – Armed Forces Hospital, Hafar Albatin, Saudi Arabia*

Correspondence should be addressed to **Mohammed Ibrahim Alsubhi**, Department of Family Medicine, National Guard Hospital, Jeddah, Saudi Arabia, email: Dr.Alsubhimo@gmail.com

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Abstract

Diabetes mellitus (DM) is marked by hyperglycemia and may develop due to insulin deficiency or reduced insulin sensitivity. The global prevalence of DM was 14% in 2024, and it is estimated to elevate significantly by 2040. DM and its complications significantly influence patients and their families' finances as well as nations' economies. The complications of diabetes involve nephropathies, retinopathies, cardiovascular diseases, and neuropathies. Diabetic nephropathy is one of the most common long-term complications occurring in patients with DM. The renin-angiotensin system (RAS) is activated by hyperglycemia in diabetic patients and contributes to the development of diabetic nephropathy. The RAS consists of two non-classical and classical axes, which are mainly enzymes and peptides. Although the activation of the intrarenal RAS in diabetes is mentioned in previous studies, the influence of hyperglycemia on RAS activation in diabetic nephropathy is not well understood. The aim of this review is to summarize existing evidence focusing on the influence of hyperglycemia on RAS activation in diabetic nephropathy patients.

Keywords: *Diabetes Mellitus, Hyperglycemia, Renin-angiotensin system, RAS, Diabetic Nephropathy*

Introduction

Diabetic nephropathy, known as diabetic kidney disease, is a serious microvascular complication of diabetes. It has a high mortality rate as it can significantly lead to end-stage renal disease (ESRD) (1, 2). By 2024, it is estimated that about 14% of the global adult population will live with diabetes (3). Nephropathy can occur due to both type 1 diabetes (T1D) and type 2 diabetes (T2D); however, a lesser percentage of people with T2D will develop ESRD (4). As T2D is more prevalent, patients with T2D account for more than half of the diabetics receiving hemodialysis (5). As per previous epidemiological studies, diabetic nephropathy may develop in 5% to 40% of patients with T2D and 25% to 40% of patients with T1D (2). Diabetic nephropathy has an early phase characterized by normal glomerular filtration rate (GFR) and normo-albuminuria. It occurs within 5–10 years and is usually associated with enlarged kidneys and glomerular and tubular hypertrophy. It is also associated with microalbuminuria, which develops within 5–15 years and is characterized by urinary excretion of 30 mg to 300 mg albumin/24 h creatinine (6).

The latter stage of diabetic nephropathy occurs within 10-20 years and is characterized by macroalbuminuria or explicit proteinuria. It is also defined by urinary excretion of albumin values more than 300 mg albumin/24 h of creatinine. As GFR continues to decrease, diabetic nephropathy may advance to ESRD in 15-25 years. ESRD typically appears 5 years following the onset of nephrotic phase proteinuria (6, 7). Multiple profibrotic and proinflammatory processes that are induced by hyperglycemia contribute to the pathogenesis of ESRD in diabetes. These processes hurt podocytes and break down the glomerular filtration barrier, enlarging the mesangial matrix, leading to tubulointerstitial fibrosis and lower GFR (4). The damage of the renal glomerular barrier results in albuminuria and worsens the impact of tubulointerstitial fibrosis (8). Intrarenal renin angiotensin system (RAS) components are upregulated in diabetic nephropathy patients, while systemic RAS components are downregulated. Thus, the intra-renal RAS is believed to play an essential role in the onset of diabetic nephropathy that is characterized by proteinuria and a progressive decline in renal function (9).

RAS includes two axes: 1- the renin, angiotensin-converting enzyme (ACE), angiotensin (Ang) II, and Ang II type 1 receptor (AT_1R), 2- (ACE2, Ang 1-7, Ang 1-9, AT_2 receptor (AT_2R), and Mas receptor (MasR) (10). An improper activation of ACE/Ang II axis and an imbalance in RAS activation play a key role in the development of kidney injury (11). Besides the primary role of Ang II as a hemodynamic mediator, it acts as a cytokine through stimulating local and systemic RAS. It also increases glomerular capillary pressure and permeability, leading to proteinuria (protein leakage into urine). Additionally, Ang II promotes kidney hypertrophy, renal cell proliferation, and excessive extracellular matrix (ECM) production, which contributes to fibrosis. It also triggers cytokine release, inflammation, and macrophage infiltration, all of which further damage the kidneys over time, potentially leading to chronic kidney disease (CKD) (7, 12, 13).

Hyperglycemia can lead to RAS activation in diabetic nephropathy patients. A recent study demonstrated that hyperglycemia induced the formation of both AT_1 R and AT_2 R and intrarenal Ang I and Ang II in diabetic murine kidneys (14). Another study showed that hyperglycemia decreased both the AT_1 R and ACE mRNA levels and increased the angiotensinogen mRNA level in the kidneys of diabetic rats (15). In addition, hyperglycemia stimulated epithelial-to-mesenchymal transition (EMT) in renal tubular cells and podocytes and resulted in renal dysfunction and fibrosis in patients with diabetes and experimental animals with diabetic nephropathy (16).

Despite these findings that confirm the activation of the intrarenal RAS in diabetes, the impact of hyperglycemia on intrarenal RAS component expressions in Diabetic nephropathy remains debatable. The aim of this review is to discuss the influence of hyperglycemia on renin-angiotensin system activation in diabetic nephropathy.

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Methods

Medline (PubMed), Scopus, and Web of Science were used in systematic research till March 9, 2025. To retrieve the synonyms of the search strategy, the MeSH database was used. Boolean operators according to the Cochrane Handbook for Systematic Reviews of Interventions were used to combine search terms by "AND" and "OR" as follows: "Hyperglycemia" OR "Postprandial hyperglycemia" AND "Renin Angiotensin System" AND "Diabetic nephropathy" OR "Diabetic Kidney Disease" OR "Diabetic Glomerulosclerosis." Summaries and duplicates of the found studies were exported and removed by EndNoteX8. Any study that discusses the influence of hyperglycemia on renin-angiotensin system activation in diabetic nephropathy and is published in peer-reviewed journals was included. All languages are included. Full-text articles, case series, abstracts, and animal studies with the related topics are included. Case reports, comments, and letters were excluded.

Discussion

Renin angiotensin system in the kidney

The RAS consists of two non-classical and classical axes, which are mainly enzymes and peptides. Their role is to control blood pressure and to balance fluids and electrolytes (17). The nonclassical RAS is formed of the ACE2-Ang 1-7/MasR and the Ang II/AT_2R axes. Angiotensin converting enzyme 2 converts Ang II into Ang 1-7 that antagonizes AT_1R when interacting with MasR (4). This stimulates a reno-protective effect in multiple kidney diseases, including acute kidney injury, glomerulonephritis, tubulointerstitial fibrosis, hypertension, and diabetic nephropathy (18). The ACE2/Ang1-7 axis often mitigates the impact of the Ang II/AT_1R axis by elevating nitric oxide and prostaglandins, promoting natriuresis, diuresis, and vasodilation, and decreasing oxidative stress (4). Nevertheless, emerging data suggests that non-classical RAS elements contribute to the therapeutic-purpose blockage of the classical system, which mitigates various kidney damage indicators, supports normal renal function, and lowers blood pressure (19).

On the other hand, the classic or systemic RAS involves the ACE/Ang II/AT_1R axis. It begins with the formation of renin by the juxtaglomerular apparatus, which transforms angiotensinogen (AGT) to Ang I, followed by the conversion of Ang I to Ang II through ACE in lung endothelial cells (20). Ang II, the primary physiological peptide in the classic RAS, stimulates reactive oxygen species (ROS) production through interaction with AT_1R. It also stimulates cell proliferation, vasoconstriction, fibrosis, oxidative stress, and hypertrophy, all of which result in kidney damage progression (21). The interstitial and intratubular regions of the nephron house all the essential components for intrarenal Ang II formation, distinguishing the renal RAS as unique (22). Renal cells independently produce renin, renin receptors, Ang receptors, and Ang II without relying on systemic RAS (7). Proximal tubular cells exhibit renin mRNA expression and renin-like activity (23). The brush border of proximal tubules highly expresses ACE mRNA and protein, with ACE also present in the fluids of proximal, distal tubular, and collecting ducts, though it is most concentrated in the proximal tubule fluid (24).

AT2R mRNA is distributed across various vascular and tubular regions of the medulla and cortex, including the proximal tubule, collecting duct, afferent arterioles, arcuate arterioles, and the outer medullary descending vasa recta (25). Additionally, ACE2 is abundantly expressed in kidney tubular cells (26), while MasR has been identified in the renal cortex, thick ascending loop of Henle, proximal tubule, collecting duct, afferent arteriole, tubular epithelium, and mesangial cells (27). The kidney is also capable of converting Ang I into Ang II, ensuring that all necessary components for intrarenal Ang II production are present throughout the nephron (4).

Renin-angiotensin system in diabetes mellitus

In diabetes mellitus, the circulating RAS is typically suppressed; however, the renal tissue RAS appears to be activated (28). It was found that protein expression and renin mRNA are elevated in proximal and juxtaglomerular tubule cells in rats with spontaneous or streptozotocin induced

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diabetes, along with a rise in Ang II production (29). The levels of renal AGT mRNA are also increased, indicating that the proximal tubule elevates AGT synthesis (28, 29).

A glucose-response element has been observed in the AGT gene promoter, and elevated extracellular glucose levels enhance AGT synthesis in a concentration-dependent manner (30). Additionally, extracellular glucose enhances AGT gene expression through reactive oxygen species in the proximal tubule (31). In mesangial cells of rats, elevated levels of glucose stimulate transforming growth factor-b (TGF-b) and Ang II (32). Ang II receptors showed a regulation in experimental models of DM. Although reduced expression of the renal AT1 receptor has been observed in some studies, downregulation of the renal AT2 receptor has been regularly reported (33, 34). It was found that streptozotocin induced DM is associated with a remarkable increase in renal renin content in the (mREN-2) 27 rat model, where tissue renin is overexpressed (34, 35). This is explained by an elevation in renin gene expression in both proximal and juxtaglomerular tubule cells. Furthermore, when (mREN-2) 27 rats were treated with streptozotocin, they showed accelerated renal glomerulosclerosis. However, the alterations in renal pathology can be undone by blockade of the AT1 receptor or inhibition of ACE (35). The renal interstitial concentrations of Ang II elevate progressively in streptozotocin induced DM, while those of NO metabolites decrease progressively (36).

Treatment with an AT1 receptor blocker further elevates Ang II levels while concurrently restoring normal concentrations of NO end products (nitrate and nitrite). These findings align with the observed downregulation of the AT2 receptor in DM, as the AT2 receptor is known to facilitate NO release (34). Consequently, a proposed model of the RAS role in DM suggests that AT2 receptors, which counteract AT1 receptor activity, are downregulated, allowing the AT1 receptor to remain unopposed. This model may support detrimental effects related to an increase in Ang II levels, including stimulation of oxygen free radical formation, renal cell proliferation and hypertrophy, increased blood pressure, insulin resistance, increased production of extracellular matrix and inhibition of its degradation, mesangial cell contraction with decreased surface area for filtration, and induction of growth factors (especially TGF-b) (34). The biosynthesis of Ang II by mesangial cells is increased by glucose (32). Ang II and glucose induce extracellular matrix formation, which could be blocked by AT1 receptor blockade (32). Additionally, TGF-b is a significant mediator of collagen formation stimulated by Ang II. In rat mesangial cells, the blockade of the AT1 receptor can inhibit the production of glucose-induced increase in TGB-b (32).

The development of Diabetic nephropathy in humans is partly mediated by Ang II via TGF-b (37). Therefore, it appears that glucose can induce Ang II, resulting in TGF-b-induced formation of extracellular matrix in DM. Furthermore, Ang II infusion has been demonstrated to cause insulin resistance, while ACE inhibitors and Ang II receptor blockers enhance insulin sensitivity (38). In patients with insulin resistance, blood vessels produce excess oxygen free radicals, which can degrade NO and induce the production of free hydroxyl radicals and hydrogen peroxide. This in turn can lead to damage to cell membranes and lipid peroxidation. Furthermore, insulin resistance enhances AT1 receptor expression, while Ang II activates NAD(P)H oxidase, leading to increased endothelial production of oxygen free radicals. AT1 receptor blockers restore normal oxygen free radical levels, enhance endothelial function, and prevent Ang-II-induced vasoconstriction in insulin-resistant rats (38).

Regulation of renin-angiotensin system by hyperglycemia in diabetic nephropathy

Diabetic nephropathy is a complex, multifactorial disease involving various pathways and mediators (7). It results from hemodynamic abnormalities, metabolic disorders, and hormonal dysregulation, particularly involving the RAS (39). Key contributors include advanced glycation end products (AGEs), TGF-β1, protein kinase C (PKC), mitogen-activated protein kinases (MAPKs), and

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reactive oxygen species (ROS), which interact and exacerbate kidney injury (40). Oxidative stress plays a significant role in diabetic nephropathy pathogenesis, as inhibition of oxidative stress has been shown to improve DN-related features (41). It results from an imbalance between oxidants and antioxidants and is a common outcome of several pathogenic pathways, including hyperglycemia (40). Increased ROS production, particularly through NADPH oxidase isoform Nox 4, leads to podocyte, mesangial, and endothelial cell damage, causing proteinuria and tubulointerstitial fibrosis (42). Additionally, oxidative stress triggers inflammatory cytokine release, worsening local and systemic inflammation (7). ROS further activates pro-fibrotic pathways, including Ang-II, PKC, and TGF-β, perpetuating oxidative damage (42).

RAS also significantly contributes to diabetic nephropathy progression, as its inhibition can slow chronic kidney disease (CKD) progression, reduce proteinuria, and preserve renal function (43). Podocytes express RAS receptors and produce RAS components, highlighting their regulation by Ang-II (43). Ang-II exerts systemic and local renal effects beyond hemodynamics, playing a key role in kidney injury via oxidative stress, inflammation, and fibrosis (13). It activates multiple pathogenic pathways, leading to cellular damage in endothelial, mesangial, epithelial, tubular, and podocyte cells (13). Despite therapeutic interventions targeting Ang-II and oxidative stress, clinical outcomes remain inconsistent (44, 45). Furthermore, the kidney maintains high intrarenal Ang-II levels, independent of systemic RAS, with glucose-induced renin and Ang-II synthesis in mesangial cells further exacerbating injury (46). High Ang-II levels increase glomerular pressure and permeability, stimulate cell proliferation, and promote ECM synthesis and inflammation (47). RAS blockade benefits diabetic nephropathy progression despite low systemic renin levels (7, 12).

In addition, inflammation plays a crucial role in DN pathogenesis (39), despite diabetic nephropathy not traditionally being classified as an inflammatory disease. Cytokines such as IL-1, IL-6, IL-18, TNF-α, and TGF-β1 are elevated in D diabetic nephropathy and correlate with disease progression (48, 49). Persistent systemic and renal inflammation contributes to diabetic nephropathy development (50), with inflammatory cell accumulation closely linked to disease severity (51). Experimental models show that reducing inflammatory cell infiltration into the kidney has protective effects (52). Additionally, inflammatory mediators contribute to EMT, leading to ECM accumulation and fibrosis (7). Upregulated chemoattractant cytokines and adhesion molecules further recruit leukocytes, perpetuating kidney injury (39).

The hyperinsulinemia caused by tissue insulin resistance and prolonged hyperglycemia can lead to upregulation of RAS components and stimulation of profibrotic and proinflammatory actions mediated by ANG II (53). This in turn results in macrovascular complications of diabetes as well as diabetic nephropathy (54). Hyperglycemia also induces renin release and elevates the expression of (pro)renin receptor, ACE, AT 1R, and AGT in rat kidneys (53, 55, 56). Additionally, angiotensin II type 2 receptor is upregulated, but this receptor seems to induce diuresis and natriuresis to counteract elevations in blood pressure (57). The upregulation of AGT expression induced by high glucose treatment in rat proximal tubule cells is alleviated by co-treatment with insulin, which functions by regulating proteins bound to the insulin response element within the AGT promoter (58, 59). It was observed that acute alterations in insulin and glucose using clamped rats lead to similar regulation of AGT in liver and adipose tissue (60). Insulin infusion led to suppression of AGT gene expression in the liver and fat of lean, but not obese, rats. On the other hand, infusion of glucose elevated AGT gene expression in the livers and fat of both lean and obese rats (53).

Additionally, hyperglycemia induced upregulation of RAS elements required for the synthesis and actions of ANG II in tissues, including adipose tissue, kidney, and liver, may precipitate hypertension associated with the metabolic syndrome as well as end-organ damage (e.g., kidney) in T2D (53). A recent study assessed, using

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a streptozotocin (STZ)-induced diabetic gerbil model, the influence of hyperglycemia on RAS and epithelial-mesenchymal transition (EMT) in the kidneys (16). Hyperglycemia activates RAS, leading to increased Ang II and ACE expression. This contributes to EMT, characterized by reduced E-cadherin and increased N-cadherin, promoting kidney fibrosis. The process involves oxidative stress, inflammation, and transforming growth factor-beta (TGF-β) signaling, ultimately leading to renal dysfunction (16).

Conclusion

In conclusion, hyperglycemia plays a crucial role in the renin-angiotensin system activation in diabetic nephropathy and kidney disease progression. The imbalance between the classical and non-classical RAS pathways contributes to renal fibrosis, inflammation, and oxidative stress. While numerous experimental studies support these mechanisms, a significant limitation remains the lack of comprehensive human studies. Further clinical research is needed to validate these findings and develop targeted therapies for diabetic nephropathy.

Disclosures

Author contributions

The authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Ethics statement

Not applicable.

Conflict of interest

The authors declare no competing interest.

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