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Review Article

Synergistic Role of Renin-Angiotensin System and Dyslipidemia in Diabetic Kidney Disease: A Mini Review

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Abstract *- Renin-angiotensin system (RAS) is a well-documented active mediator in progressive diabetic kidney disease (DKD). Ancillary to hyperglycemia association with dyslipidemia appears to impact the initiation and progression of renal injury in diabetes, giving a link between plasma lipoproteins and angiotensin II in the causation of renal injury under a hyperglycemic setup. Activation of local RAS convoluted in hyperlipidemia-mediated renal injury results in the extracellular matrix deposition in the tubular interstitium, suggesting that the major effector peptide (Ang II) of the RAS pathway and lipoproteins does not act independently but acts synergistically facilitating the progression of chronic kidney disease. Appreciating the relationship between Angiotensin Converting Enzyme (ACE) Insertion/Deletion (I/D) genotypes or any other ACE gene polymorphism and dyslipidemia with DKD opens up the scope for early recognition of diabetic patients with a high risk of DKD. Systematic in-depth observational and ethnic population studies considering ACE Inhibitors and anti-lipid drugs in relation to ACE genotypes are warranted to help understand the role of the ACE gene that appears to be a major contributor to the complex mechanism involved and the environment in the form of lifestyle in diabetic kidney disease complication.*

Keywords *- Renin-angiotensin system, Diabetic kidney disease, Hyperglycemia, Dyslipidemia, ACE gene polymorphism.*

1. Introduction

Diabetic kidney disease (DKD), a chief microvascular complication, is a common cause of chronic kidney disease (CKD) that eventually leads to End-Stage Renal Disease [ESRD], necessitating dialysis or kidney transplantation. Of late, it is a major health concern as 40% of type 2 diabetic (T2D) individuals with poor or uncontrolled diabetes develop DKD allied with high morbidity and mortality. Further, the lack of economical and effective renal care for patients with CKD also contributes to the global healthcare burden. Escalating the incidence of DKD parallels the steep rise in the prevalence of diabetes globally, projected to rise to 366 million by 2030 [1,2].

DKD is histologically characterized by mesangial expansion, glomerular basement membrane thickening, interstitial fibrosis, podocyte loss and reduced endothelial cell fenestration. In advanced cases, there is an infiltration of immune cells such as macrophages and T-lymphocytes. The early clinical features of DKD are associated with glomerular hyperfiltration, an increase of micro-albuminuria (≥30 to 299mg/g creatinine) to macroalbuminuria (≥ 300 mg/g creatinine) and a decrease in glomerular filtration rate (GFR). The discerned patho-mechanisms in the occurrence and progression of DKD are metabolic abnormalities, hemodynamic changes, environmental factors, oxidative stress (OS), inflammatory milieu and genetic predisposition [3]. This review primarily focused on detecting the link between the Renin-Angiotensin System (RAS) and dyslipidemia in the pathogenesis of DKD.

Prevailing literature suggests that Ang II acts via its receptors (AT_1R and AT_2R), a crucial element of RAS, critical in regulating blood pressure and fluid electrolyte homeostasis, which advocates progressive renal impairment in DKD. Angiotensin I-converting enzyme (ACE) produced in blood vessels, lungs and kidneys mediates the conversion of angiotensin I to angiotensin II (Ang II) through the inactivation of bradykinin. Thus, RAS genes are important genetic susceptible factors for both diabetes and diabetic kidney disease [4,5].

2. Renin Angiotensin System and Diabetes

β-cell failure and insulin resistance (IR) are the two main features in the manifestation of type 2 diabetes. β-cell failure is a prerequisite in the development of T2D, and decline in the β-cell function/loss of β-cell mass are key determinants in T2D progression. Existing literature suggests RAS may be responsible for the reduced secretion of insulin [6]

Hyperglycemia under diabetic conditions causes an upsurge in the tissue AngII stimulating "OS, glomerular hyperfiltration, endothelial damage, thrombosis, inflammation and vascular remodeling" [7]. Activation of the renin-angiotensin system and higher production of Ang II results in inhibiting the insulin signal transduction pathway, a potential cause of diabetes mellitus. It prevents the phosphorylation of insulin receptor substrate-1 (IRS-1) and diminished glucose uptake via GLUT4, giving rise to IR. It augments reactive oxygen species (ROS) production, ensuing pancreatic β-cells damage and impairment in insulin secretion through reduced blood flow of the pancreas due to vasoconstriction. Longstanding hyperglycemia and fat promote inflammation, OS, and apoptosis of the pancreatic β-cells [8]. Aldosterone, the other component of RAS, also decreases insulin secretion in a mechanism that involves OS. Besides, *in vitro* and *vivio* studies have shown improved insulin sensitivity with a decline in the Ang II and aldosterone levels or AT1R and mineralocorticoid receptor inhibition. Clinical trial studies on angiotensin-converting enzyme inhibitors (ACEI) or Ang II receptor blockers (ARBs) have demonstrated the role of RAS in the pathogenesis of IR in type 2 diabetes [9]. It has been revealed that ACEI and ARBs have beneficial effects on patients with diabetic complications [10].

3. Renin-Angiotensin System and Diabetic Kidney Disease

The role of RAS in DKD was established in 1980 in streptozotocin (STZ) induced diabetic animal models, which disclosed that the glomerular hemodynamic changes are allied with proteinuria and resemble the pathological features of human DKD, including glomerulosclerosis. These studies revealed that inappropriate activation of RAS at local renal tissue increases Ang II levels accelerating renal and vascular injury [11]. Further, through their experimental studies, Zatz et al. (1986) showed normalization of glomerular pressure, reduced albumin excretion and the chance of glomerulosclerosis after enalapril treatment, an ACE inhibitor. Thus, it suggests that the diabetic condition stimulates RAS causing the activation of AT_1R via Ang II, leading to increased glomerular hydrostatic pressure, proteinuria and structural injury [12].

In addition, it is known that Ang II contributes to both hemodynamic and non-hemodynamic effects such as proinflammatory, proliferative and profibrotic activities in the pathogenesis of DKD. Activation of the AT_1R receptor causes the release of transforming growth factor-beta (TGF-β), a proinflammatory and profibrotic molecule that leads to renal fibrosis, a recognized cause of glomerulosclerosis [3]. Under hyperglycemic conditions, tubular epithelial cells in a RAS-dependent manner are responsible for macrophage recruitment that promotes extracellular matrix formation causing renal fibrosis [13,14].

Zhernakova et al. (2006) in type 1 diabetes observed that T-cell activation and proliferation are fostered by RANTES and T-helper type 1 chemokine [15]. It is known that Ang II and ROS are generated through macrophages and lymphocytes during inflammation, and elevated Ang II levels in DKD activate immune cells following chemokine production triggering kidney injury. In support of this, elevated ACE and Ang II concentrations were observed in immunostained interstitial and tubular cells by Mezzano et al. (2003) in DKD patients. Under diabetic conditions, tubular cells are the direct target for high glucose, which augments Ang II secretion and angiotensinogen gene expression. Thus, the disrupted renal function in diabetes is, to some extent, due to the prominent levels of ACE and Ang II together with high glucose and inflammatory mediators (NFκB, MCP-1) [16,17,18].

Among the other probable factors contributing to DKD are disturbances in lipid metabolism, clinically termed dyslipidemia. Dyslipidemia is a condition associated with decreased serum concentration of high-density lipoprotein (HDL), increased cholesterol, small and dense low-density lipoprotein (LDL) particles, triglycerides (TG) and triglyceride-rich lipoprotein (apolipoprotein B), a common feature of diabetes and its complication DKD [58].

4. Dyslipidemia in Diabetes and Diabetic Kidney Disease

It is well-accepted that alterations in lipid metabolism results from IR and defective insulin action. Insulin facilitates the uptake of free fatty acids (FFAs) by striated muscle and adipose tissue. Lipase gets activated under a hyperglycemic milieu resulting in the release of increased levels of FFAs from the adipose tissue. Therefore, the flux of FFAs clinically manifests as hypertriglyceridemia due to excessive production of very low-density lipoprotein (VLDL) and apoB lipoproteins [20]. Reduced lipoprotein lipase activity under IR primes the TG-rich lipoproteins buildup in the plasma. Further, VLDL-cholesterol instigates cascades of conversions; eventually, the glycation and oxidation of small and dense LDL bring about vascular and renal cellular dysfunction [21].

Higher serum TG levels decreased HDL levels, and enhanced glycation and LDL oxidation are common

observations in T2D patients [22]. Bhowmik et al. (2018) observed a linear trend of increasing risk ranging from 2-4fold for high TC, TG and low HDL among glucose-intolerant, type 2 diabetic and prediabetic individuals [23].

Progressive renal impairment is linked with proteinuria and goes hand in hand with lipoprotein transport anomalies owed to various pathogenic mechanisms. Vaziri et al. (2001 & 2003), through his Imai rat model of spontaneous focal glomerulosclerosis (FGS), have shown that altered regulation of HMG-CoA and ACAT-2 in the hepatocytes influences the control of lipid metabolism with advanced FGS [24,25]. Scheuer et al. (2000), in their trials on uninephrectomized rat models, observed hyperlipidemia-dependent glomerular and tubulointerstitial infiltration and exacerbation of glomerulosclerosis suggesting a link between dyslipidemia and OS in the development of renal damage [26]. The collection of advanced glycated plasma proteins, lipoproteins, and immunoglobulins in the extracellular matrix affects renal function and exacerbates glomerulosclerosis [27]. In experimental models of renal disease, it has been noted that feeding on high cholesterol diet advances glomerulosclerosis [28]. Evidence supports that dyslipidemia is significantly linked with developing and advancing diabetic and non-diabetic kidney disease [29,20,31]. The relation between hyperlipidemia and glomerular injury is not a new concept; an era ago, Moorhead et al. (1982) observed a connection between hyperlipidemia and glomerular capillary injury, suggesting that the continuous filtration of lipids and lipoproteins promotes the progression of chronic renal injury [32]. In both type 1 and type 2 diabetic patients, dyslipidemia is not ancillary to renal disease. An unfavorable lipid profile was noticed at the early albuminuria stage, irrespective of the glomerular filtration functioning[33]. Ravid et al. (1998) observed that high TC levels were significantly accompanied by a higher prevalence of microalbuminuria and cardiovascular events among 574 patients with T2D and normal kidney function at baseline [34]. Tolonen et al. (2008), in patients with Type 1 diabetes, report an upsurge in TC, VLDL, LDL and TG levels with abnormal albumin excretion rate [35]. A post hoc analysis carried out by Kajingulu et al. (2018) reports that 70% of the T2D patients with abnormal albuminuria had atherogenic dyslipidemia, mainly low levels of HDL-cholesterol contributing to cardiovascular disease and renal disease progression [36]. Lu et al., 2022 reported that low levels of LDL-c/ApoB ratio were positively linked with DKD risk among type 2 diabetic subjects [37].

4.1. Mechanism of Lipid-Induced Renal Injury

Wellmann, in 1970 identified that lipid nephrotoxicity plays a pivotal role in the advancement of DKD; earlier studies have shown that under the hyperglycemic environment, dyslipidemia promotes glomerulosclerosis [57]. Diabetic rat model experiments have illustrated hypercholesterolemia accelerates albuminuria, and lipid-lowering therapy improves glomerulosclerosis in Zucker rats. Hyperlipidemia promotes the generation of ROS, such as superoxide and hydrogen peroxide, by monocytes and mesangial cells, accounting for 30-40% of the total glomerulus. Macrophage infiltration in the glomeruli occurs due to oxidized LDL (OxLDL) binding to scavenger receptors in mesangial cells and podocytes. Further, macrophages become foam cells via the uptake of OxLDL and activate the TNF-α, TGF-β and IL-6 pathways. ROS serve as a chemoattractant for macrophages and T-lymphocytes, causing an upsurge in the podocyte apoptosis of endothelial cells and mesangial expansion, subsequently leading to renal injury [21].

5. The link between ACE and dyslipidemia

Higher concentrations of Ang II (as a result of elevated systemic or localized ACE levels) contribute to OS favoring OxLDL formation, resulting in cell injury and renal lesions. As a result of glomerular capillary hypertension, the glomerular permeability of macromolecules increases and causes mesangium lipid and tubular lipoprotein overload. Further, Ang II stimulates and enhances the release of chemokines and cytokines, increasing lipid infiltration and accumulation in macrophages and promoting glomerular and tubular-interstitial injury (Figure 1) [4]. *In vivo* and *in vitro* studies by Ni et al. (2013) demonstrate that activation of local RAS is involved in hyperlipidemia-mediated renal injuries resulting in the extracellular matrix deposition in the tubular interstitium, suggesting that the major effector peptide of the RAS pathway Ang II and lipoproteins does not act independently but acts synergistically facilitating the progression of CKD [39].

Replicating the results of animal and cell-based studies that are carried out under controlled conditions helps in only speculating the outcome at the human population level as complex interactions interfere through different mechanisms. In other words, studying the complex diseases in the human population is arduous as there is no control over genetics or lifestyle.

6. ACE gene Insertion/Deletion Polymorphism and Diabetic Kidney Disease

Unraveling the basis for the variation in the occurrence of the type of diabetic complications in diabetic patients aids in the prevention or therapeutic aspects of the disease complications. Among the various environmental and genetic causes, dyslipidemia and Ang II emerge as important markers in the manifestation of T2D and DKD. Several observational and experimental studies have not been given much attention to population-based studies. As DKD aetio-pathophysiology is multifactorial in nature, numerous complex interactions involved in it are required to be understood. In the present review, we attempted to gather the literature about the role of lipids and Ang II in the susceptibility of DKD.

It is well documented that individuals genetically differ with respect to Ang II levels based on the genetic alterations in the ACE gene. Of the many genetic variants of the ACE gene on 17q23, intron 16, an Insertion/Deletion (I/D) polymorphism is well established with low and high levels of ACE. This is a common polymorphism with variable genotype frequency in diverse ethnic groups with genotype-dependent differences in circulating and renal ACE levels [40].

A meta-analysis on ACE I/D gene polymorphism by Lakkakula et al. (2019) encompassing 45 publications (from 1994 to 2018) with data of 6124 diabetic Kidney disease and 2492 type 2 diabetic patients of Asian and Caucasian origin reported a significant contribution of the D allele to DKD susceptibility, in other words, showed a role of ACE I/D polymorphism in the development of T2D to DKD [40]. Their univariate analysis was limited to gene polymorphism and the disease condition. A recent study of ours (Mahwish et al., 2020) from India, apart from supporting the conclusion of the above meta-analysis, also showed. It increased and decreased the risk for DKD patients of DD and ID genotypes with dyslipidemia to develop DKD more than the patients with normal lipid profiles with corresponding genotypes, exemplifying gene and environmental interaction in DKD pathogenesis [4]. Tseng et al. (2010) found a positive association of atherosclerotic risk factors such as hypertension, smoking, dyslipidemia, and obesity with ACE genotypes among Taiwanese T2D patients with albuminuria [41]. Nagi et al. (1998) also showed the relation between circulating levels of ACE with plasma TG and TC concentrations among T2D Pima Indians. [42]. Thus, the DD genotype could be a credible factor for varied ACE levels and a promoter of dyslipidemia in a hyperglycemic setting culminating in renal injury.

7. DKD patient's Therapeutic Response to ACE inhibitors and Ang II receptor blockers: Do ACE genotypes influence it?

Progression from microalbuminuria to macroalbuminuria elevates an individual's risk towards renal and cardiovascular diseases. There is a direct relation between the level of albuminuria and progression towards ESRD and mortality in diabetic patients [43].

ACE inhibitors (ACEIs) have been the mainstay treatment for DKD since 1986; they decline the production of Ang II, resulting in a decrease in the glomerular permeability to urinary albumin leading to the falling of protein in the urine. ACEIs and ARBs are effective in dipping albuminuria and decelerating kidney disease progression both in diabetic and non-diabetic subjects [5]. However, there is an inter-individual disparity in reno-protective therapy among the patients. Evidence from the literature suggests ACE I/D polymorphism could be a contributing aspect to a certain extent to the response variation though there is inconsistency (Table1). Understanding this disparity is warranted in different ethnic populations.

Further, experimental studies suggest that adding statins to the ACEIs and ARBs may have a beneficial effect in reducing albuminuria and have better reno protection than RAS blockade alone in rats with overt nephropathy [56]. Henceforth it can be surmised that RAS blockade and statins are not independent components of treatment regimens in managing dyslipidemia and proteinuria in relation to DKD. As there is an increase in the number of cases with DKD, advancing cost-effective therapeutic strategies for these individuals is of major public health concern.

8. Conclusion

RAS has been known for more than a century and is widely known for its multitasking nature. Hyperglycemia-dependent variations in the intracellular Ang II levels are observed in DKD and cardiomyopathy, promoting cardiovascular disorders and hypertension. ACEIs and ARBs are the standard management strategy for the above disease condition. However, in order to address the drug response variation and effective therapy assessing the levels of ACE or screening for the genetic variants of the ACE gene apart from lipid profile may help in better management of diabetes-related complications or may contribute to the development of new pharmacological approaches.

In conclusion, the present mini-review focused on the relationship between the RAS pathway, particularly the ACE gene and dyslipidemia as one of the underlying mechanisms involved in DKD in patients with chronic diabetes mellitus. Literature shows a strong association between the ACE I/D genotypes and dyslipidemia with DKD which opens up the scope for an early diagnosis of patients prone to DKD. Further, systematic in-depth observational ethnic population studies considering ACE and anti-lipid drugs in relation to ACE genotypes are warranted to help understand the role of a gene that appears to be a major contributor to the complex mechanism involved and the environment in diabetic complications.

Author Contributions

Umme Najiya Mahwish: Literature search, writing an original draft and editing the manuscript. Swetha and Babi Heer: Literature search and critical inputs. Parveen Jahan: Writing the original draft and editing and approving the manuscript. Rudrama Devi and Sree Bhushan Raju: critically revised the manuscript.

References

[1] Radica Z Alicic, Michele T Rooney, and Katherine R Tuttle, "Diabetic Kidney Disease: Challenges, Progress, and Possibilities," *Clinical Journal of the American Society of Nephrology*, vol. 12, no. 12, pp. 2032–2045, 2017. [CrossRef] [Google Scholar] [Publisher Link]

[2] Sarah Wild et al., "Global Prevalence of Diabetes: Estimates for the Year 2000 and Projections for 2030," *Diabetes care*, vol. 27, no. 5, pp. 1047–1053, 2004. [CrossRef] [Google Scholar] [Publisher Link]

[3] Andy KH Lim, "Diabetic Nephropathy - Complications and Treatment," *International Journal of Nephrology and Renovascular Disease*, vol. 7, pp. 361–381, 2014. [CrossRef] [Google Scholar] [Publisher Link]

[4] Mahwish Umme Najiya et al., "Link between ACE I/D Gene Polymorphism and Dyslipidemia in Diabetic Nephropathy: A Case-control Study from Hyderabad, India," *Indian Journal of Nephrology*, vol. 30, no. 2, pp. 77–84, 2020. [CrossRef] [Google Scholar] [Publisher Link]

[5] Tanuj Chawla, Deepika Sharma, and Archana Singh, "Role of the Renin Angiotensin System in Diabetic Nephropathy," *World Journal of Diabetes*, vol. 1, no. 5, pp. 141–145, 2010. [CrossRef] [Google Scholar] [Publisher Link]

[6] Gijs H Goossens, "The Renin-Angiotensin System in the Pathophysiology of Type 2 Diabetes," *Obesity Facts*, vol. 5, no. 4, pp. 611–624, 2012. [CrossRef] [Google Scholar] [Publisher Link]

[7] Zohreh Rahimi, Mahmoudreza Moradi, and Hamid Nasri, "A Systematic Review of the Role of Renin Angiotensin Aldosterone System Genes in Diabetes Mellitus, Diabetic Retinopathy and Diabetic Neuropathy*," Journal of Research in Medical Sciences*, vol. 19, no. 11, pp. 1090–1098. 2014. [Google Scholar] [Publisher Link]

[8] Ming-Sheng Zhou, and Ivonne Hernandez Schulman, "Prevention of Diabetes in Hypertensive Patients: Results and Implications from the VALUE trial," *Vascular Health and Risk Management*, vol. 5, no. 1, pp. 361–368, 2009. [CrossRef] [Google Scholar] [Publisher Link]

[9] James Matthew Luther, and Nancy J. Brown, "The Renin-Angiotensin-Aldosterone System and Glucose Homeostasis," *Trends in pharmacological sciences*, vol. 32, no. 12, pp. 734–739, 2011. [CrossRef] [Google Scholar] [Publisher Link]

[10] Patricia C. Underwood, and Gail K. Adler, "The Renin Angiotensin Aldosterone System and Insulin Resistance in Humans," *Current hypertension reports*, vol. 15, no. 1, pp. 59–70, 2013. [CrossRef] [Google Scholar] [Publisher Link]

[11] Susan B. Gurley, and Thomas M. Coffman, "The Renin-Angiotensin System and Diabetic Nephropathy," *Seminars in Nephrology*, vol. 27, no. 2, pp. 144–152, 2007. [CrossRef] [Google Scholar] [Publisher Link]

[12] R. Zatz et al., "Prevention of Diabetic Glomerulopathy by Pharmacological Amelioration of Glomerular Capillary Hypertension," *Journal of Clinical Investigation*, vol. 77, no. 6, pp. 1925–1930, 1986. [CrossRef] [Google Scholar] [Publisher Link]

[13] G. H. Tesch, "MCP-1/CCL2: a New Diagnostic Marker and Therapeutic Target for Progressive Renal Injury in Diabetic Nephropathy," *American Journal of Physiology-Renal Physiology*, vol. 294, no. 4, pp. F697–F701, 2008. [CrossRef] [Google Scholar] [Publisher Link]

[14] Takashi Wada et al., "Monocyte Chemoattractant Protein-1: Does it play a Role in Diabetic Nephropathy?," *Nephrology Dialysis Transplantation*, vol. 18, pp. 457-459, 2003. [CrossRef] [Google Scholar] [Publisher Link]

[15] A. Zhernakova et al., "Genetic Variants of RANTES are Associated with Serum RANTES Level and Protection for Type 1 Diabetes," *Genes and Immunity*, vol. 7, pp. 544-54, 2006. [CrossRef] [Google Scholar] [Publisher Link]

[16] Bernardo Rodríguez-Iturbe et al., "Role of Immunocompetent Cells in Nonimmune Renal Diseases," *Kidney International*, vol. 59, no. 5, pp. 1626-1640, 2001. [CrossRef] [Google Scholar] [Publisher Link]

[17] Tanuj Chawla, Deepika Sharma, and Archana Singh, "Role of the Renin Angiotensin System In Diabetic Nephropathy," *World journal of diabetes*, vol. 1, no. 5, pp. 141-145, 2010. [CrossRef] [Google Scholar] [Publisher Link]

[18] Sergio Mezzano et al., "Renin-angiotensin System Activation and Interstitial Inflammation in Human Diabetic Nephropathy," *Kidney International*, vol. 64, pp. S64-S70, 2003. [CrossRef] [Google Scholar] [Publisher Link]

[19] Kamal Dwebeh, Abdullah Cheikh Ibrahim, and Maher Madi, "Left Ventricular Dysfunction in Patients with Liver Disease," *SSRG International Journal of Medical Science*, vol. 8, no. 10, pp. 1-5, 2021. [CrossRef] [Publisher Link]

[20] Szu-chi Chen, and Chin-Hsiao Tseng, "Dyslipidemia, Kidney Disease, and Cardiovascular Disease in Diabetic Patients," *The Review of Diabetic Studies*, vol. 10, no. 2-3, pp. 88–100, 2013. [CrossRef] [Google Scholar] [Publisher Link]

[21] Daiji Kawanami, Keiichiro Matoba, and Kazunori Utsunomiya, "Dyslipidemia in Diabetic Nephropathy," *Renal Replacement Therapy*, vol. 2, no. 16, 2016. [CrossRef] [Google Scholar] [Publisher Link]

[22] Milagros J. Jacobs et al., "Prevalence and Control of Dyslipidemia among Persons with Diabetes in the United States," *Diabetes Research and Clinical Practice*, vol. 70, no. 3, pp. 263–269, 2005. [CrossRef] [Google Scholar] [Publisher Link]

[23] Bishwajit Bhowmik et al., "Serum Lipid Profile and Its Association with Diabetes and Prediabetes in a Rural Bangladeshi Population," *International Journal of Environmental Research and Public Health*, vol. 15, no. 9, pp. 1944, 2018. [CrossRef] [Google Scholar] [Publisher Link]

[24] N.D. Vaziri, K. Liang, and J.S. Parks, "Acquired Lecithin-Cholesterol Acyltransferase Deficiency in Nephrotic Syndrome," *American Journal of Physiology-Renal Physiology*, vol. 280, no. 5, pp. F823–F828, 2001. [CrossRef] [Google Scholar] [Publisher Link]

[25] Nosratola D. Vaziri, Tadashi Sato, and Kaihui Liang, "Molecular Mechanisms of Altered Cholesterol Metabolism in Rats with Spontaneous Focal Glomerulosclerosis," *Kidney International*, vol. 63, no. 5, pp. 1756–1763, 2003. [CrossRef] [Google Scholar] [Publisher Link]

[26] Hartmut Scheuer et al., "Oxidative Stress in Hyperlipidemia- Induced Renal Damage," *American Journal of Physiology-Renal Physiology*, vol. 278, pp. F63-F74, 2000. [CrossRef] [Google Scholar] [Publisher Link]

[27] Sho-ichi Yamagishi, and Takanori Matsui, "Advanced Glycation end Products, Oxidative Stress and Diabetic Nephropathy," *Oxidative Medical and Cellular Longevity*, vol. 3, vo. 2, pp. 101–108, 2010. [CrossRef] [Google Scholar] [Publisher Link]

[28] Bertram L. Kasiske et al., "The Renal Injury of Diet-Induced Hypercholesterolemia in Rats," *Kidney International*, vol. 37, no. 3, pp. 880–891, 1990. [CrossRef] [Google Scholar] [Publisher Link]

[29] Michal Herman-Edelstein et al., "Altered Renal Lipid Metabolism and Renal Lipid Accumulation in Human Diabetic Nephropathy," *Patient-Oriented and Epidemiological Research*, vol. 55, no. 3, pp. 561–572, 2014. [CrossRef] [Google Scholar] [Publisher Link]

[30] M. C. Bulbul et al., "Disorders of Lipid Metabolism in Chronic Kidney Disease," *Blood Purification*, vol. 46, no. 2, pp. 144–152, 2018. [CrossRef] [Google Scholar] [Publisher Link]

[31] Aleix Cases, and Elisabet Coll, "Dyslipidemia and the Progression of Renal Disease in Chronic Renal Failure Patients," *Kidney Internationa*l, vol. 68, pp. S87–S93, 2005. [CrossRef] [Google Scholar] [Publisher Link]

[32] J. F. Moorhead et al., "Lipid Nephrotoxicity in Chronic Progressive Glomerular and Tubulo-Interstitial Disease," *The Lancet*, vol. 320, no. 8311, pp. 1309–1311, 1982. [CrossRef] [Google Scholar] [Publisher Link]

[33] Roberto Trevisan, Alessandro R Dodesini, and Giuseppe Lepore, "Lipids and Renal Disease," *Journal of the American Society of Nephrology*, vol. 17, no.4, pp. S145–S147, 2006. [CrossRef] [Google Scholar] [Publisher Link]

[34] Mordchai Ravid, Lily Neumann, and Michael Lishner, "Plasma Lipids and the Progression of Nephropathy in Diabetes Mellitus Type 2: Effect of ACE Inhibitors," *Kidney International*, vol. 47, no. 3, pp. 907–910, 1995. [CrossRef] [Google Scholar] [Publisher Link]

[35] N. Tolonen et al., "Relationship between Lipid Profiles and Kidney Function in Patients with Type 1 Diabetes," *Diabetologia*, vol. 51, no. 1, pp. 12–20, 2008. [CrossRef] [Google Scholar] [Publisher Link]

[36] M. Kajingulu, Francois et al, "Albuminuria Status and Patterns of Dyslipidemia among Type 2 Diabetes Black Patients Managed at a Tertiary Health-care Hospital: A Post hoc Analysis," *Saudi Journal of Kidney Diseases and Transplantatio*, vol. 29, no. 3, pp. 649-657, 2018. [CrossRef] [Google Scholar] [Publisher Link]

[37] Lu Chun-Feng et al, "Comparisons of the Relationships between Multiple Lipid Indices and Diabetic Kidney Disease in Patients with Type 2 Diabetes: A Cross-Sectional Study," *Frontiers in Endocrinology*, vol. 13, 2022. [CrossRef] [Google Scholar] [Publisher Link]

[38] Meteb Altaf et al., "Monitoring Diabetic Foot by Designing a New Smart Sole," *SSRG International Journal of Pharmacy and Biomedical Engineering*, vol. 7, no. 3, pp. 15-20, 2020. [CrossRef] [Publisher Link]

[39] Ni Jie et al, "Activation of Renin-Angiotensin System is Involved in Dyslipidemia-Mediated Renal Injuries in Apolipoprotein E knockout mice and HK-2 cells," *Lipids in Health and Disease*, vol. 12, no. 49, 2013. [CrossRef] [Google Scholar] [Publisher Link]

[40] Bhaskar VKS Lakkakula et al., "Genetic Association of ACE gene I/D Polymorphism with the Risk of Diabetic Kidney Disease; a Meta-Analysis," *Journal of Nephropathology*, vol. 8, no. 4, 2019. [CrossRef] [Google Scholar] [Publisher Link]

[41] Chin-Hsiao Tseng, Ching-Ping Tseng, and Choon-Khim, "Chong Joint Effects of Hypertension, Smoking, Dyslipidemia and Obesity and Angiotensin-Converting Enzyme DD Genotype on Albuminuria in Taiwanese Patients with Type 2 Diabetes Mellitus," *Clinical Biochemistry*, vol. 43, no. 7-8, pp. 629-634, 2010. [CrossRef] [Google Scholar] [Publisher Link]

[42] D.K. Nagi et al., "Angiotensin-1-Converting Enzyme (ACE) Gene Polymorphism, Plasma ACE levels, and their Association with the Metabolic Syndrome and Electrocardiographic Coronary Artery Disease in Pima Indian," *Metabolism*, vol. 47, no. 5, pp. 622-626, 1998. [CrossRef] [Google Scholar] [Publisher Link]

[43] Zohreh Rahimi, "ACE insertion/deletion (I/D) Polymorphism and Diabetic Nephropathy," *Journal of Nephropathology*, vol. 1, no. 3, pp. 143-151, 2012. [CrossRef] [Google Scholar] [Publisher Link]

[44] Hans-Henrik Parving et al., "Effect of Deletion Polymorphism of Angiotensin Converting Enzyme Gene on Progression of Diabetic Nephropathy during Inhibition of Angiotensin Converting Enzyme: Observational Follow up Study," *BMJ*, vol. 313, pp. 591–594, 1996. [CrossRef] [Google Scholar] [Publisher Link]

[45] G. Penno et al, "Effect of Angiotensin-Converting Enzyme (ACE) Gene Polymorphism on Progression of Renal Disease and the Influence of ACE inhibition in IDDM Patients: Findings from the EUCLID Randomized Controlled Trial. EURODIAB Controlled Trial of Lisinopril in IDDM," *Diabetes*, vol. 47, no. 9, pp. 1507–1511, 1998.[CrossRef] [Google Scholar] [Publisher Link]

[46] Jacobsen Peter et al., "Genetic Variation in the Renin-Angiotensin System and Progression of Diabetic Nephropathy," *Journal of the American Society of Nephrology*, vol. 14, no. 11, pp. 2843–2850, 2003. [CrossRef] [Google Scholar] [Publisher Link]

[47] Steen Andersen et al, "Renoprotective Effects of Losartan in Diabetic Nephropathy: Interaction with ACE Insertion/Deletion Genotype?," *Kidney International*, vol. 62, pp. 192–198, 2002. [CrossRef] [Google Scholar] [Publisher Link]

[48] Steen Andersen et al, "Long-term Renoprotective Effects of Losartan in Diabetic Nephropathy: Interaction with ACE Insertion/Deletion Genotype?," *Diabetologia Praktyczna*, vol, 4, no. 3, pp. 211-218, 2003. [Google Scholar] [Publisher Link]

[49] Sung Kyu Ha et al, "ACE DD Genotype is more Susceptible than ACE II and ID Genotypes to the Antiproteinuric effect of ACE Inhibitors in Patients with Proteinuric Non-Insulin-Dependent Diabetes Mellitus," *Nephrology Dialysis Transplantation*, vol. 15, no. 10, pp. 1617–1623, 2000. [CrossRef] [Google Scholar] [Publisher Link]

[50] Masakazu Haneda et al., "Antiproteinuric Effect of Candesartan Cilexetil in Japanese Subjects with Type 2 Diabetes and Nephropathy," *Diabetes Research and Clinical Practice*, vol. 66, no. 1, pp. 87–95, 2004. [CrossRef] [Google Scholar] [Publisher Link]

[51] W. Y. So et al., "Angiotensin-Converting Enzyme (ACE) Inhibition in type 2, Diabetic Patients - Interaction with ACE Insertion/Deletion Polymorphism," *Kidney International*, vol. 69, no. 8, pp. 1438–1443, 2006. [CrossRef] [Google Scholar] [Publisher Link]

[52] Hans-Henrik Parving et al, "ACE Gene Polymorphism and Losartan Treatment in Type 2 Diabetic Patients with Nephropathy," *Journal of the American Society of Nephrology*, vol. 19, no. 4, pp. 771–779, 2008. [CrossRef] [Google Scholar] [Publisher Link]

[53] Balneek Singh Cheema et al., "Endothelial Nitric Oxide Synthase Gene Polymorphisms and Renal Responsiveness to RAS Inhibition Therapy in type 2 Diabetic Asian Indians," *Diabetes research and clinical practice*, vol. 99, no. 3, pp. 335-42, 2013. [CrossRef] [Google Scholar] [Publisher Link]

[54] Neerja Aggarwal et al, "Role of Angiotensin Converting Enzyme and Angiotensinogen Gene Polymorphisms in Angiotensin Converting Enzyme Inhibitor-Mediated Antiproteinuric Action in Type 2 Diabetic Nephropathy Patients," *World Journal of Diabetes*," vol. 8, no. 3, pp. 112–119, 2017. [CrossRef] [Google Scholar] [Publisher Link]

[55] Abdur Raza et al, "Association of Angiotensin Converting Enzyme Gene Polymorphism with Diabetic Nephropathy in Patients Using Lisinopril," *Indian Journal of Pharmacy and Pharmacology*, vol. 9, no. 2, pp. 96-102, 2022. [CrossRef] [Google Scholar] [Publisher Link]

[56] Carla Zoja et al, "Adding a Statin to a Combination of ACE Inhibitor and ARB Normalizes Proteinuria in Experimental Diabetes, which Translates into full Renoprotection," *American Journal of Physiology-Renal Physiology*, vol. 299, no. 5, pp. F1203–F1211, 2010.[CrossRef] [Google Scholar] [Publisher Link]

[57] K. F. Wellmann, and B.W. Volk, "Renal Changes in Experimental Hypercholesterolemia in Normal and in Subdiabetic Rabbits. II. Long term Studies," *Laboratory Investigati*on, vol. 24, no. 2, pp. 144–155, 1971. [Google Scholar] [Publisher Link]

[58] Rey F. Rosario, and Sharma Prabhakar, "Lipids and Diabetic Nephropathy," *Current Diabetes Reports*, vol. 6, pp. 455-462, 2006. [CrossRef] [Google Scholar] [Publisher Link]

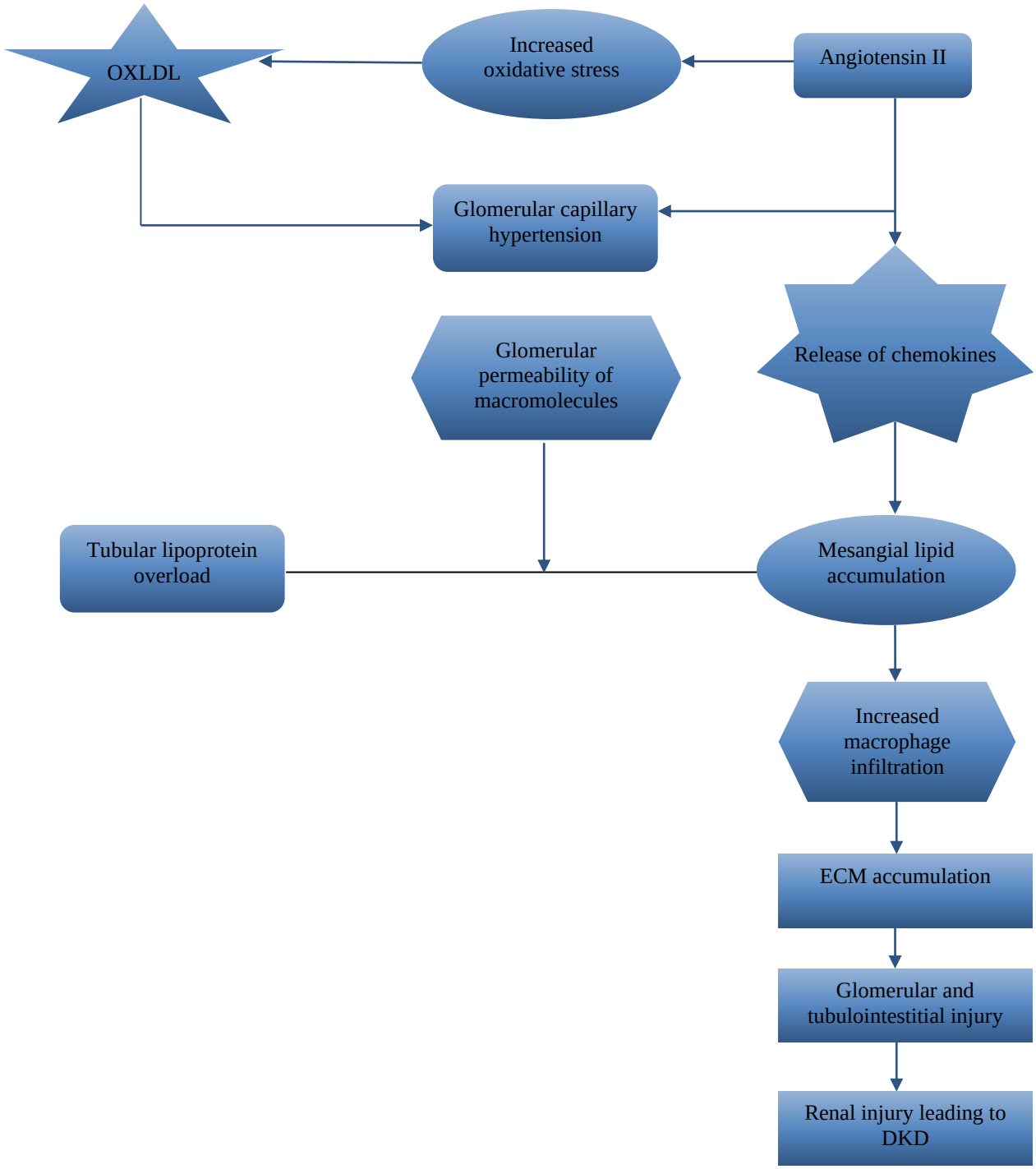

Fig. 1 Link between Angiotensin II and lipoprotein in the development of renal injury in DKD

OxLDL=Oxidised LDL, ECM=extracellular matrix, DKD=diabetic kidney disease

Table 1. Association studies of the ACE I/D polymorphism and response to ACEI or ARB therapy

Disease and sample size	Ethnicity	Study durations (months)	Therapy ACEI/ARBs	Drug	Response	Authors (year)	Reference
T1D (35)	Caucasian	84	ACEIs	Captopril	Fast progression and higher residual proteinuria in the DD genotype	Parving et al. (1996)	[44]
T1D (530)	Caucasian	24	ACEIs	Lisinopril	albuminuria reduction was more in individuals with the II genotype	Penno et al. (1998)	[45]
T1D (60, 169)	Caucasian	7	ACEIs	Captopril/ Captopril, lisinopril, enalapril	D allele augmented development of DKD	Jacobsen et al. (1998, 2003)	[46]
T1D (54)	Caucasian	4	ARBs	Losartan	Change in the reduction of proteinuria was not observed	Andersen et al (2002, 2003)	[47.48]
T2D (83)	Asian (Korean)	3	ACEI	Benazepril, perindopril	albuminuria reduction was more in DD genotype patients	Ha et al. (2000)	[49]
T2D (127)	Asian (Japanese)	3	ARBs	Candesartan	Change in the reduction of proteinuria was not observed	Haneda et al. (2004)	[50]
T2D (2089)	Asian (Chinese)	44.6	RAAS inhibitors	RAAS inhibitors	Elevated risk of reduced renal function with DD genotype	So et al. (2006)	[51]
T2D (1435)	Mixed	40.8	ARBs	Losartan	Reduction reaching ESRD	Parving et al. (2008)	[52]
T2D (490)	Asian (Indian)	36	ACEIs/ARB		A better renoprotective effect was found among II genotype individuals/ better reno-protective response was noted with DD genotype patients	Cheema et al. (2013)	[53]
T2D (270)	Asian (Indian)	6	ACEIs	Ramipril	Response of DKD patients was independent of ACE I/D polymorphisms	Neerja Agarwal et al. (2017)	[54]
DKD (121)	Asian (Indian)	2	ACEIs	Lisinopril	Response of DKD patients was dependent on ACE I/D polymorphism	Razaq et al. (2022)	[55]

T1D: Type 1 diabetes, T2D: Type 2 diabetes, DKD: Diabetic kidney disease, ACEIs: Angiotensin-converting enzyme inhibitors, ARB: Angiotensin receptor blockers