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Polymorphisms in Glucose Metabolism-related Genes as Indicators of Diabetic Nephropathy Risk: A Narrative Review

Mohsen Mehrabzadeh[1], Hassan Ravari[1], Gholamhosein Kazemzadeh[1], Sahel Baraty Darbandy[2] and Susan Darroudi[1] and Hanie Mahaki[1*]

[1]Vascular and Endovascular Surgery Research Center, Mashhad University of Medical Sciences, Mashhad, Iran
[2]Department of Operating Room, Neyshabur University of Medical Sciences, Neyshabur, Iran

[*]**Correspondence Author:** Hanie Mahaki, Vascular and Endovascular Surgery Research Center, Mashhad University of Medical Sciences, Mashhad, Iran, E-mail: Hanieh.Mahaki@gmail.com, mahakih2@mums.ac.ir

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Abstract

Diabetic nephropathy (DN) is one of the most common chronic and progressive diabetes complications. It causes most end-stage renal disease (ESRD) worldwide due to its high mortality rate. To prevent or delay DN, high-risk patients must be identified early. Individuals with diabetes develop it due to hereditary and environmental causes. Several single nucleotide polymorphisms (SNPs) have been identified in different genes, which significantly contribute to genetic susceptibility to DN. An extensive search was conducted on Google Scholar, Scopus, Web of Sciences, and PubMed between 2004 until May 2024 We utilized publications, including original articles, Review, Systematic review and meta-analysis studies, that were published in English. Current studies revealed that variations in genes related to glucose metabolism are thought to be associated with DN. This review is focused on the various studies about the association between different polymorphisms in glucose metabolism-related genes and DN. Aldose Reductase (AKR1B1), Glucose transporter-1 (GLUT-1), Glucokinase regulatory protein (GKRP), Receptor of Advanced glycation end products (RAGEs), and Transcription factor 7-like 2 (TCF7L2) are the most important glucose metabolism-related genes in DN. Identifying gene variants at a biomarker level could enable the detection of patients who are at an elevated risk for DN. This may assist in early prevention, diagnosis, and treatment.

Keywords: Diabetic Nephropathy, Polymorphism, Glucose metabolism gene

Abbreviations

Activator Protein 1 (AP-1); Activin Receptor-Like Kinase 1 (ALK1); Adenosine Triphosphate (ATP); Adiponectin (ADIPOQ); Advanced Glycation End products (AGEs); Albumin-to-Creatine Ratio (ACR); Aldo-Keto Reductase Family 1 Member B

(AKR1B1); GR (Glutathione Reductase); Aldose Reductase (ALR2); Angiotensin II (Ang II); Centers for Disease Control (CDC); Chronic Kidney Disease (CKD); Connective Tissue Growth Factor (CTGF); Cyclooxygenase (COX); Deoxyribonucleic Acid (DNA); Diabetes Mellitus (DM); Diabetic Nephropathy (DN); Diacylglycerol (DAG); Diacylglycerol/Protein kinase C (DAG-PKC); Dihydroxyacetone Phosphate (DHAP); Angiotensin II Receptors, (ATR); Endothelin-1 (ET-1); End-Stage Renal Disease (ESRD); estimated Glomerular Filtration Rate (eGFR); Extracellular Matrix (ECM); Extracellular signal-Regulated Kinase (ERK); Genetics of Diabetes Audit and Research Tayside (Go-DARTs); Genome Wide Association Studies (GWAS); Glomerular Filtration Rate (GFR); Glucokinase (GK); Glucokinase Regulator (GCKR); Glucokinase Regulatory Protein (GKRP); Glucose Transporter 1 (GLUT1); Glucose-6-phosphate (G-6-P); Glutathione Disulfide (GSSG); Glyceraldehyde 3-phosphate (GA3P); Haemophilus Aegyptius (Hae); Helicobacter pylori CH4 (HpyCH4); High-Mobility Group (HMG); Hyperglycemia (HG); Inducible Nitric Oxide Synthase (iNOS); Insulin-like Growth Factor-1 (IGF-1); Intercellular Adhesion Molecule 1 (ICAM-1); Interleukin 6 (IL-6); Interleukin 8 (IL-8); Interleukin-1 beta (IL-1β); Janus kinase/ Signal Transducers and Activators of Transcription (JAK/STAT); Kilo Dalton (kDa); Linkage Disequilibrium (LD); Lysyl Oxidase (LOX); Matrix Metalloproteinases (MMP); Mitogen-Activated Protein Kinase (MAPK); Monocyte Chemoattractant Protein 1 (MCP1); NADPH-Oxidase (NOX); Nicotinamide Adenine Dinucleotide Phosphate (NADPH); Nitric Oxide (NO); Nitric Oxide Synthase (NOS); Non-Alcoholic Fatty Liver Disease (NAFLD); Non-Insulin-Dependent Diabetes Mellitus (NIDDM); Nuclear Factor Kappa B (NF-κB); endothelial Nitric Oxide Synthase (eNOS); Phosphatidylinositol 3-Kinase (PI3K); Prostaglandins (PG); Protein Kinase B (PKB, or Akt); Protein kinase C (PKC); Reactive Oxygen Species (ROS); Nicotinamide Adenine Dinucleotide (NADH); Receptor of Advanced Glycation End products (RAGEs); Renin-Angiotensin System (RAS); Renin-Angiotensin-Aldosterone System (RAAS); Serum Amyloid A (SAA); Single Nucleotide Polymorphisms (SNPs); Solute carrier family 2 member 1 (SLC2A1); Sorbitol Dehydrogenase (SDH); Suppressor of Mothers Against Decapentaplegic (SMAD); T-cell Factor/Lymphoid Enhancer binding factor Family (TCF/LEF); Sodium/Glucose cotransporter 2 (SGLT2); Transcription Factor 4 (TCF4); Transcription Factor 7-like 2 (TCF7L2); Transforming Growth Factor beta (TGF-β); Reduced Glutathione (GSH); Tumor Necrosis Factor alpha (TNF a); Type 2 Diabetes (T2D); Upstream Stimulatory Factor (USF); Vascular Cell Adhesion Molecule 1 (VCAM-1 or CD106); Vascular Endothelial Growth Factor (VEGF); Wingless-related integration site (Wnt); Xanthomonas badrii (Xba)

Introduction

Diabetes mellitus (DM) is a chronic metabolic syndrome that over time inflicts significant damage to blood vessels and results in chronic complications such as nephropathy, neuropathy, retinopathy, etc [1]. The International Diabetes Federation estimated over 537 million diabetic cases worldwide in 2021.The number of diabetic individuals has been regularly increasing for the past few decades, so that by 2045 this number might rise to approximately 783 million. Complications of diabetes lead to higher mortality rates, lower quality of life, and account for a major challenge to the health care system regarding the economic burden of diabetic cases [2]. Diabetic nephropathy (DN) is a common microvascular complication of DM, defined by hyperglycemia-induced renal dysfunction, often with persistent albuminuria and a gradual decline in the estimated glomerular filtration rate (eGFR). In other words, microvascular complications of DM mostly target the kidney and cause glomerular changes. The Centers for Disease Control and Prevention (CDC) state that DM is the leading cause of chronic kidney disease (CKD) and end-stage renal disease (ESRD) [3]. Other causes of CKD include hypertension, genetic basis, glomerulonephritis, etc. DN can result from either type 1 or type 2 DM with a similar renal risk and an equal time period between proteinuria and ESRD in both types [4]. It has been reported that up to 50% of diabetic cases will develop CKD. Approximately 700 million people, or 9% of the global population, are affected by CKD, and kidney replacement therapy is required in nearly four million cases [5]. DN and ESRD, as a global public health problem, impose an enormous financial burden on the healthcare system annually [6].

The pathophysiology of DN is complicated, and precise mechanisms remain unknown, but various causes such as hyperglycemia (HG), autoimmune processes, insulin resistance, genetics, etc., have been proposed. Chronic HG is the primary cause of DN. It produces reactive oxygen species (ROS) and activates downstream pathways such as

advanced glycation end products (AGEs) formation, pro-tein kinase C, hexosamine and hexosamine [7]. HG stimu-lates the renal cells to release chemokines and cytokinessuch as VEGF, TGF-β, MCP-1, and IL-6, which can lead tofibrosis and increased vascular permeability. This leads topodocytopathy, which causes albuminuria. The conse-quence of intraglomerular hypertension is proteinuria [8].Generally, the histological changes in DN are characterizedby expansion of the mesangial cells, thick-ening of glomeru-lar and tubular basement membrane, and endothelial dis-ruption, which eventually results in the loss of nephrons(Figure 1) [9]. DN is asymptomatic in early stages. As a re-sult, most patients are not diagnosed until the disease hasprogressed. The primary characteristics of DN include pro-gressive proteinuria, hypertension, glomerulosclerosis, andreduced GFR. In fact, DN is characterized by consistently(at least 3 months) reduced eGFR < 60 (mL/min/1.73 m2)and increased urine albu-min excretion (albumin-to-crea-tine ratio [ACR] ≥ 30 mg/g) (10). Due to the considerablemorbidity and mortali-ty rates and high treatment costs ofDN, screening and monitoring DN cases are crucial. For ex-ample, optimizing glycemia and controlling hypertensioncan hinder the progression of DN [7].

Risk factors for DN include modifiable and non--modifiable risk factors. Hyperglycemia, oxidative stress, hypertension, smoking, obesity and hyperlipidemia contribute to the progression of DN, and all are modifiable. As a result, implementing intensive management is critical in order to prevent renal cell disruption. On the other hand, genetic background, ethnicity, and diabetes duration, which play a key role in the developing of DN, cannot be modified [11]. The role of heredity and genetic make-up in the susceptibility of diabetic cases to DN has been studied by researchers for a long time [12,13]. The risk of proteinuria in diabetic patients is significantly related to the renal function of their parents. It has been shown that irrespective of glycemic control, 46% of the offspring were found to have DN if both parents had the disease. On the other hand, if only one parent had proteinuria, only 23% of the offspring progressed to DN, and 14% can progress to DN if both parents had no proteinuria [14]. Family-based linkage studies of DN have mapped this trait to certain parts of chromosomes, like sites on chromosomes 18q, 3q, 7p, 22q and 2p. It shows that these loci are highly penetrant Mendelian genes with rare genetic variants that have substantial effects [15].

Genetic studies were conducted to identify genes (alleles) that increase susceptibility to DN and comprehend the pathophysiology of DN at the molecular and mechanistic level. These studies focused mainly on the association between clinical phenotypes of DN and genetic variants such as single nucleotide polymorphisms (SNPs) [16]. Numerous candidate gene polymorphisms of DN have been pinpointed with development genetic methods such as genome-wide association studies (GWAS) and linkage and candidate gene studies. GWAS is a method used to investigate the correlation between a particular gene and a disease. This is done by analyzing a large number of DNA samples and examining the existence of sequence variants using high-density SNP genetic markers. Over the last decades, GWAS have emerged as a potent method for detecting genetic risk factors for DN [13]. Mooyaart et al. carried out a comprehensive meta-analysis and determined 24 genetic variants in 16 genes most likely to cause DN [17]. Recently, Tziastoudi et al. conducted a meta-analysis of genetic association studies in order to clarify the role of genetic background in the development of DN and identified 66 genetic variants located in 53 genes [12].

DN, the main complication of DM, is undoubtedly associated to glucose metabolism. Therefore, it is believed that DN is associated with changes in the genes involved in glucose metabolism. This article aims to examine the most significant glucose metabolism gene polymorphisms associated to DN.

The purpose of this article is to review the most effective glucose metabolism gene polymorphisms associated with DN, according to their functions in the development of DN. As a result, we have provided an overview of recent research. In Table 1, we categorized and discussed these susceptibility genes based on their SNPs. In this study, we are investigating this matter for the first time.

Table 1: The susceptibility genes related to glucose metabolism associated with DN

Gene	SNP	OR	Study type	Population type	Race	Sample size	P value	Location	Ref.
AKR1B1	rs759853	1.52 (1.26, 1.84)	Meta	DN	Caucasians & Asians (Different population)	7435	< 0.0001	7q35	(33)
	rs759853	1.63(1.02-2.61)	CC	DKD	Brazil	1005	0.03		(92)
	(AC)n dinucleotide repeat polymorphism at the 5′-end of the aldose reductase gene	1.40 (1.07, 1.84)	Meta	T1DM	Caucasian	2751	< 0.05		(93)
GLUT1	rs841853	-	CC	T2DM	West Indians	631	0.027	1p34.2	(39)
	rs1385129	-	CC	T2DM	West Indians	631	0.01		(39)
	rs841847	1.73 (1.17-2.56)	Meta	T2DM	Caucasians	598	0.006		(49, 94)
	rs841853	1.74 (1.18-2.55)					0.005		(94)
	rs12407920	2.01 (1.17-3.45)					0.01		(94)
GCKR	rs1260326	1.18 (1.05–1.33)	Cohort	T2DM	Chinese	6072	< 0.05	2p23.3	(57)
	rs1260326	1.12	Cohort	T2DM	European	2097	4.27×10–2		(54)
	rs780094	1.71 (1.17-2.49)	CC	T2DM	Chinese	318	0.048		(56)
	rs1799884	1.73 (1.24–2.40)	Cohort	T2DM	Chinese	6072	< 0.05		(57)
RAGE	G1704T	2.93 (1.34-6.41)	CC	T2DM	Japanese	181	0.0057	6p21.32	(95)
	rs1800625	1.51 (1.04-2.20)	CC	T2DM	Chinese	347	0.03		(96)
	2184A/G	0.46 (0.22-0.92)	CC	T2DM	Chinese	868	0.028		(67)
	374T/A	2.36 (1.1-5.6)	CC	T1DM	Egyptian	50	<0.001		(71)
	rs2070600	1.4 (1.01-1.95)	CC	T2DM	Chinese	347	0.04		(96)
TCF7L2	rs7903146	2.19 (1.69-2.83)	CC	T2DM	Caucasians	1355	<0.001	10q25.2-q25.3	(84)
	rs12255372	1.45 (1.1-1.91)	CC	T2DM	Egyptian	100	< 0.05		(97, 98)
	rs7903146	-	Meta	T2DM	Indian	205	0.049		(99)
	rs11196218	1.37 (1.06–1.78)	CC	T2DM	Chinese	898	0.0051		(91)

Abbreviations: AKR1B1, Aldo-Keto Reductase Family 1 Member B; CC, Case Control; DKD, Diabetic Kidney Disease; DN, Diabetic Nephropathy; GCKR, Glucokinase Regulatory Protein; GLUT1, Glucose Transporter 1; OR, Odds Ratio; RAGE, Advanced Glycosylation End-Product Specific Receptor; SNP, Single-Nucleotide Polymorphism; T1DM, Type 1 Diabetes; T2DM, Type 2 Diabetes; TCF7L2, Transcription Factor 7 Like 2.

Selection and search strategy of the literature

An extensive search was conducted on Google Scholar, Scopus, Web of Sciences, and PubMed between 2004 until May 2024. We utilized 398 publications, including original articles, Review, Systematic review and meta-analysis studies, that were published in english with human filter, using the Medical Subject Headings (MeSH) phrases "Diabetic Nephropathies" AND "Polymorphism, Single Nucleotide" AND "Glucose Metabolism Disorders".

Genetic variants related to glucose metabolism

Research has established that many genes play a significant role in the development of DN, alongside various environmental factors. In this regard, numerous genes related to glucose metabolism have been evaluated for their potential relationship with DN, including several SNPs which are associated with susceptibility genes for the condition. It's observed that different ethnic groups may experience varying levels of risk associated with specific genes in individuals affected by diseases such as DN [18-21]. Therefore, below is a discussion of several genes related to glucose metabolism implicated in DN (Table 1).

Aldose Reductase

Aldose Reductase (AKR1B1) is a member of the aldo-keto reductase superfamily that acts as a cytosolic enzyme on the rate-limiting step of the polyol pathway and catalyzes the conversion of glucose to sorbitol in the presence of NADPH. This gene is located on chromosome 7q35 and extends over ~18 kb. Protein of Aldose reductase consists of 316 amino acids and weighs 3500 Daltons. It presents in the majority of the tissues affected by DM. Also, toxic aldehydes generated by reactive oxygen species (ROS) are reduced by AKR1B1. Various mechanisms have been suggested to elucidate the process by which hyperglycemia-induced lesions in various tissues are induced by AKR1B1 activity [22]. The polyol pathway is a two-step process that reduces glucose to sorbitol and then converts it to fructose. Hyperglycemia stimulates activation of the polyol pathway by production of glutathione. Subsequently, glutathione levels decline in response to a drop in NADPH levels. Therefore, osmotic stress caused by the buildup of excess sorbitol and oxidative stress resulting from a drop in the NADPH/-$NADP^+$ ratio and reduced NAD^+ levels contribute to the development of DN. Also, sorbitol, due to its hydrophilic and polyhydroxy structure, cannot diffuse easily through renal cell membranes, causing osmotic stress and DN. Finally, it may be inferred that AKR1B1 activation in the polyol pathway can lead to the generation of ROS, causing oxidative stress and DN (Figure 2) [23,24]. It demonstrated that administration of AR inhibitors can halt the development of DN. It lends credence to the hypothesis that the upregulation of the AKR1B1 gene could be one of the several risk factors associated with the development of DN.

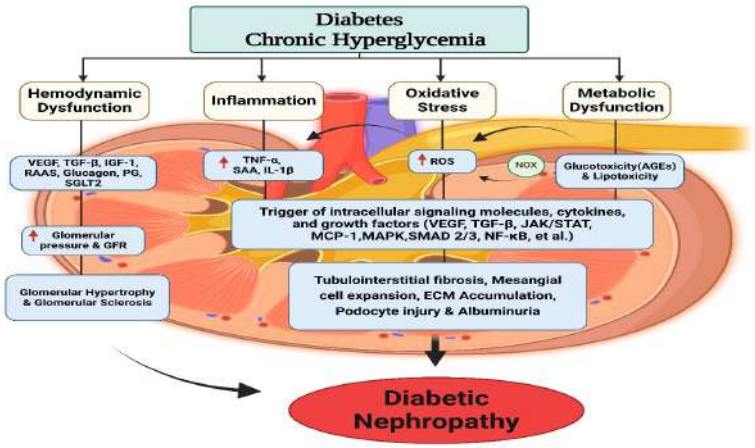

Figure 1: The pathophysiology of DN

The pathophysiology of DN involves several mechanisms, as hyperglycemia caused by diabetes triggers various harmful processes within the kidneys. These processes can be generally categorized into hemodynamic, metabolic, inflammatory, and oxidative stress, which are the primary contributors to the disease's development. This added glucose burden, along with increased oxidative stress, triggers a detrimental cascade that leads to tubular fibrosis and the development of DN. Abbreviations: VEGF, Vascular Endothelial Growth Factor; TGF-B, Transforming Growth Factor Beta; IGF-1, Insulin-like Growth Factor-1; RAAS, Renin-Angiotensin-Aldosterone System; PG, Prostaglandins; SGLT2, Sodium/Glucose Cotransporter 2; GFR, Glomerular Filtration Rate; TNF-a, Tumor Necrosis Factor alpha; SAA, serum amyloid A; IL-1B, Interleukin-1 beta; ROS, Reactive Oxygen Species; NOX, NADPH Oxidase; AGEs, advanced glycation end products; JAK-STAT, Janus kinase/ Signal Transducers and Activators of Transcription; MCP-1, monocyte chemoattractant protein 1; MAPK, mitogen-activated protein kinase; SMAD 2/3, suppressor of mothers against decapentaplegic 2/3; NF-kB, nuclear factor kappa B; ECM, extracellular matrix.

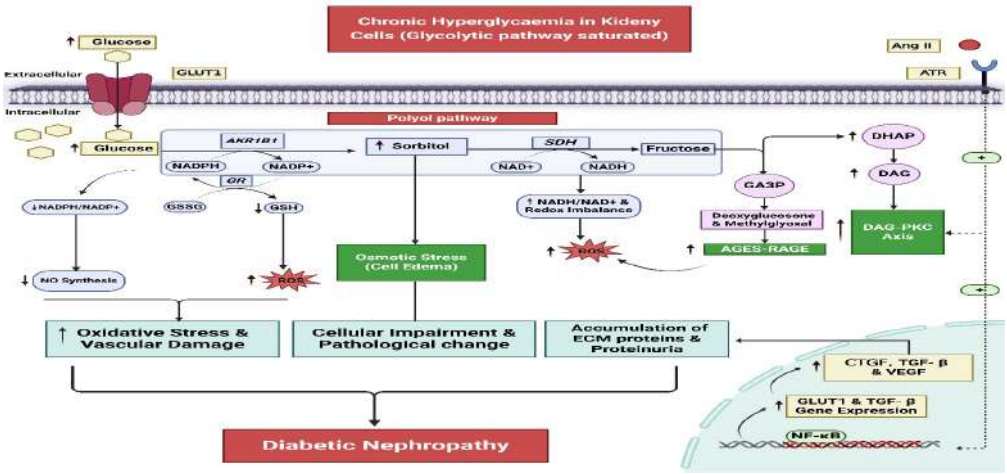

Figure 2: GLUT1 and AKR1B1 Pathway involved in the development of DN

Elevated blood sugar levels trigger the polyol pathway, producing glutathione, which decreases when NADPH levels fall. This leads to osmotic stress and oxidative stress, causing DN. Fructose produced through the polyol pathway is phosphorylated, producing fructose-3-phosphate, which is converted into 3-deoxyglucosone and methylglyoxal, which create AGEs. The DAG-PKC pathway controls vascular function, controlling endothelial permeability, vasoconstriction, extracellular matrix synthesis, cell proliferation, angiogenesis, cytokine activation, and leukocyte adhesion. Activation of DAG-PKC disrupts glomerular blood flow, causing albuminuria and promoting extracellular matrix accumulation. GLUT1 transports glucose in mesangial cells, stimulating signaling pathways that promote glomerulosclerosis. Synthesis of Ang II and TGF-β enhances GLUT1 gene expression, increasing glucose flow and contributing to glomerulosclerosis. Abbreviations: AGES - RAGE, Advanced Glycation End products - Receptor of Advanced Glycation End products; AKR1B1, Aldo-Keto Reductase Family 1 Member B; ANGII, Angiotensin II; ATR, Angiotensin II Receptors; CTGF, Connective Tissue Growth Factor; DAG, Diacylglycerol; DAG-PKC, Diacylglycerol-Protein Kinase C; DHAP, Dihydroxyacetone Phosphate; GA3P, Glyceraldehyde 3-Phosphate; GLUT 1, Glucose Transporter 1; GR, Glutathione Reductase; GSH, Reduced Glutathione GSSG, oxidized glutathione; NADH, nicotinamide adenine dinucleotide; NADPH, nicotinamide adenine dinucleotide phosphate; NF-KB, Nuclear Factor Kappa B B. NO, Nitric oxide; ROS, Reactive Oxygen Species; SDH, Sorbitol dehydrogenase; TGF-B, Transforming Growth Factor Beta; VEGF, Vascular Endothelial Growth Factor.

Most research indicates an association between elevated risk of quick onset or heightened incidence of diabetes complications and polymorphisms in the AKR1B1 gene [25,26]. First, *Ko et al.* [27] found seven alleles at the locus of the (AC)n dinucleotide repeat sequence upstream of the AKR1B1 gene. Multiple studies have shown a correla-

tion between the "Z-2" (AC)n and a higher incidence of DN [28,29]. ´5ALR2 was identified as a polymorphism that was located 2.1 kb upstream of the transcription start site of AKR1B1. It is demonstrated that there is an association between DN and ´5-ALR2 in Caucasian patients with DM [30]. At position 106 of the AKR1B1's promoter region, a second polymorphism has been found. It is associated with DN in DM cases [25,31,32]. The authors determined that their meta-analyses offered more compelling evidence for the involvement of the C-106T polymorphism compared to the $(CA)_n$ microsatellite in DN [25]. *Wenpeng Cui et al.* carried out a meta-analysis which showed strong associations between the rs759853 polymorphism and the susceptibility to DN in DM cases [33]. The association between DN and the C-106T polymorphism is unclear at the molecular level. It might be directly in the transcription process of the gene or in linkage disequilibrium with another marker. The polyol pathway is typically active solely under hyperglycemic conditions. As a result, for patients exhibiting inadequate glycemic control, the action of AR may be more significant than for those with optimal glycemic control. It has been shown that Glucose transporters can controls gene expression of AKR1B1, activity with polyol accumulation and and increased total and active PKCalpha, and GLUT1 in mesangial cells in vitro, which lead to stimulation of matrix protein synthesis [34].

Glucose transporter-1

The primary facilitative glucose transporter in glomerular mesangial cells is glucose transporter 1 (GLUT1). It is a uniporter protein encoded by the SLC2A1 gene in humans. The SLC2A1 gene contains 10 exons that span 33,802 base pairs and is located on the p arm of chromosome 1 in position 34.2. A 54.1 kDa protein made up of 492 amino acids is produced by the gene [35]. The transport of glucose across the kidney cells is facilitated by GLUT1. The degree of GLUT1 expression is typically correlated with the rate of cellular glucose metabolism, and it is found in high concentrations in the mesangial cells of the glomeruli [36].

GLUT1 is primarily found in the ascending thick limb of Henle's loop within the renal tubule, vascular smooth muscle cells, and mesangial cells of the glomerulus. GLUT1 expression undergoes early changes in diabetes. The activation of B1 and PKCα and the polyol pathway are triggered by the increased glucose metabolic flux that results from GLUT1 overexpression. PKC activation can induce AP-1 and result in an increase in fibronectin expression and the accumulation of ECM. Experimental evidence indicates that hypertensive glomerulopathy may be related to GLUT1 [37]. Elevated ambient glucose cause an increase in GLUT1 expression, especially in mesangial cells. In a hyperglycemic environment, TGF-β and GLUT1 are two proteins that are enhanced in glomerular mesangial cells and can affect each other's expression (Figure 2) [38].

Numerous case-control studies have suggested an association between GLUT1 polymorphisms and DN. Various studies on SNPs related to GLUT1 genes have been conducted for XbaI (intron 2) concerning rs841853, Enh2-1 regarding rs841847, Enh2-2 for rs841848, HaeIII (exon 2) for rs1385129, and HpyCH4V for rs710218 [39]. *Ng et al.* demonstrated that the susceptibility to DN in type 1 diabetes was correlated with SNPs at the GLUT1 (XbaI-intron 2 and HaeIII SNPs-exon 2) [40]. *Wenpeng Cui et al.* carried out a meta-analysis that showed XbaI, Enh2, and HaeIII SNPs in the GLUT1 gene may be genetic susceptibility to DN. In all genetic models, XbaI SNP (rs841853) elevated DN risk with significant differences [41]. Also, another meta-analysis revealed a substantial correlation between DN and the SLC2A1 XbaI polymorphism in the GLUT1 gene [42].

The AA genotype of rs841847 in the GLUT1 putative enhancer elements is identified as a risk genotype [40], while the TT genotype in the 5' promoter region (rs710218) is associated with DN [43]. The Haell and Enh2 SNP1 genotypes increased the risk of DN in the Tunisian population. rs1385129 is a polymorphism that has been identified as a risk factor for DN in various cohorts, including the Tunisian [44] and Kurdish populations [45]. Although some case-control studies on GLUT1 gene variations and DN have shown contradictory results [46-48], the presence of GLUT1 SNPs may be a particularly significant factor in DN [49]. The association between DN and the GlUT1 polymorphisms remains ambiguous at the molecular level. For example, the enhancer-2 SNP of GLUT1 is located within a proposed binding site for USF transcription factors, which may control gene expression in reaction to elevated glucose lev-

els and play a critical role in controlling GLUT1 expression in diabetes. It is notable that GLUT1 can control intracellular glucose metabolism pathways such as glycolysis. One of the main regulatory enzymes in glycolysis is Glucokinase. Glucokinase is regulated by glucokinase regulatory protein.

Glucokinase regulatory protein

Glucokinase (hexokinase IV or ATP: D-glucose-6-phosphotransferase, EC 2.7.1.2) is one of four types of hexokinase with special characteristics. Glucokinase (GK) is found in the cytoplasm and catalyzes the first steps of glycolysis. It converts glucose into glucose-6-phosphate. It is mostly expressed in pancreatic β-cells and liver cells, contributing to glucose homeostasis [50]. The kinetic activity of GK increases as blood glucose levels rise, which in turn stimulates insulin secretion and maintains glucose homeostasis by mediating G6P production. An alternative method of enhancing hepatic GK activity is to disrupt the binding between glucokinase regulatory protein (GKRP) and GK. GKRP is a liver-specific protein and is primarily synthesized in the hepatocyte and pancreatic islet β-cells. During fasting, GKRP regulates hepatic GK with high affinity at 5 mmol/l glucose concentrations, inactivating GK after sequestering it in the nucleus. In the postprandial state, GK separates from GKRP and moves to the cytoplasmic space, where it helps glucose become phosphorylated [51]. Its inhibitory impact is counteracted by fructose 1-phosphate and intensified by fructose 6-phosphate. GKRP is encoded by glucose metabolism-related genes, which are mapped to chromosome 2p23.3. GKRP has been identified as a diabetes susceptibility gene [52], and numerous investigations have been implemented to investigate the correlation between renal complications in T2D and GKRP. Large-scale GWAS have shown that the GKRP gene is associated with CKD and a decrease of renal function. GCK and GKRP collaborate closely to regulate blood glucose levels effectively. Mutations in the GCK and GKRP genes can disturb the equilibrium of the GCK/GKRP complex, resulting in irregular glucose levels and hyperglycemia [53].

Gene variations of GKRP were reported to be associated with many clinical symptoms, such as familial combined hyperlipidemia, coronary artery disease, ischemic stroke, T2DM, and DN. *The Genetics of Diabetes Audit and Research Tayside* (Go-DARTs) study assessed the relationship between 16 candidate gene and eGFR in 3,028 individuals with T2DM. The P446 L variant of rs1260326 in GKRP was found to be correlated with an elevated baseline eGFR, particularly in individuals with albuminuria, suggesting a relationship between GKRP polymorphisms and DN. The SNP rs1260326 (C > T) is a missense mutation located in exon 15 of GKRP, causing a substitution of proline with leucine at position 446 [54]. rs780094 represents a SNP located in the noncoding area of the GKRP gene. It exhibits strong linkage disequilibrium (LD) with rs1260326. *Yan et al*. determined that the A allele of rs780094 in GKRP was related to DN; however, the genotype was not significant [55]. *Yi-Ying Liu et al*. investigated that CT + TT genotype in GKRP rs780094 is a risk factor for T2DM complicated with albuminuria at the genetic level [56]. *Ke Wang et al*. performed a prospective cohort study and demonstrated that T allele carriers of GKRP rs1260326 were at high risk for DN in Chinese patients with T2DM [57]. The pleiotropy of the GKRP rs780094 polymorphism is substantially correlated with metabolic diseases, such as T2DM, dyslipidemia, NAFLD, and DN. The rs780094 variant is suspected to affect the expression of the GKRP gene; however, its precise mechanism of action is still unknown. It is believed that the transition from C to T may lead to the replacement of an amino acid, potentially influencing the function of GCKR; however, the role of GCKR in relation to urinary protein requires additional investigation. Clinical evidence indicates that this variant disrupts hepatic triglyceride and glucose metabolism and compromises pancreatic β-cell function in a variety of populations [58]. It has been shown that Advanced glycation end products impaired glucokinase activity resulted in islet dysfunction within murine pancreatic islets. In fact, glucokinase is downregulated by advanced glycation end products [59].

Receptor of Advanced Glycation End Products

Advanced glycation end products (AGEs) emerge when glucose and other glycation inducers bind to proteins, nucleic acids, and lipids. In fact, they are heterogeneous molecules originating from the nonenzymatic results of interactions between glucose or other saccharide derivatives and proteins or lipids. AGEs are organic compounds synthesized in living organisms, exhibiting a diverse range of struc-

tural and functional properties [60]. AGEs could accumulate in the mesangial cells, glomerular basement membrane, endothelial cells, and podocytes in individuals with diabetes and/or ESRD. AGEs are believed to contribute to the pathophysiology of DN by multifactorial mechanisms, including the formation of oxidative stress and the excessive synthesis of different growth factors and cytokines. Moreover, new studies suggest that the interaction between AGEs and the renin-angiotensin system (RAS) may contribute to DN. The activation of the RAS induces reactive oxygen species (ROS) formation, which subsequently increases the synthesis of growth factors and cytokines by renal cells. About 50%-80% of exogenous AGEs are eliminated through the kidneys; however, AGEs continue to accumulate in the kidneys. Hyperglycemia causes more AGEs to form, which can build up in the kidneys and harm various kidney cells [61].

In addition to being markers of inflammation, hyperglycemia and oxidative stress, AGEs also contribute to progressing of DN by interacting with AGE receptors (RAGE) [62]. Among the numerous types of AGE receptors, RAGE serves as a signal transducing receptor for AGEs, potentially mediating the inflammatory responses induced by AGEs. This protein, encoded by a gene on chromosome 6, is a 394-amino-acid transmembrane protein belonging to the immunoglobulin superfamily. The protein RAGE, which ranges from 44 to 55 kDa in size, is made up of an outer section comprising a V-domain and two C-domains that interact with numerous ligands, a transmembrane helix, and a cytoplasmic tail essential for intracellular signaling triggered by RAGE. The RAGE gene is widely expressed in various cells and tissues, including smooth muscle cells, monocytes/macrophages, endothelial cells, vasculature, brain tissue, heart and lung. In the kidneys, almost every kind of cell expresses RAGE, with a higher concentration observed in podocytes compared to the endothelial and mesangial cells found in the glomeruli [63,64].

Activation of RAGE results in elevated expression of NADPH oxidase, NOS, and COX; these processes worsen and amplify the inflammatory response. The AGE-RAGE axis and RAS are involved in the development of DN. The increase in RAGE expression is associated with damage in endothelial cells due to its interaction with AGEs. Different ligands can attach to RAGE, which results in abnormal inflammation, stimulation of the renin-angiotensin-aldosterone system, triggering of TGF-β signaling, promotion of irregular angiogenesis, and activation of adhesion signaling. The ligands' binding to RAGE activates numerous intracellular signaling pathways that regulate diverse cellular processes, including cell movement and cytoskeleton arrangement. Therefore, RAGE plays an essential role in the progression of different renal conditions [65]. Growing proof suggests that the activation of RAGE hinders the function of microvascular barriers, which results in increased permeability of endothelial cells (Figure 3) [66].

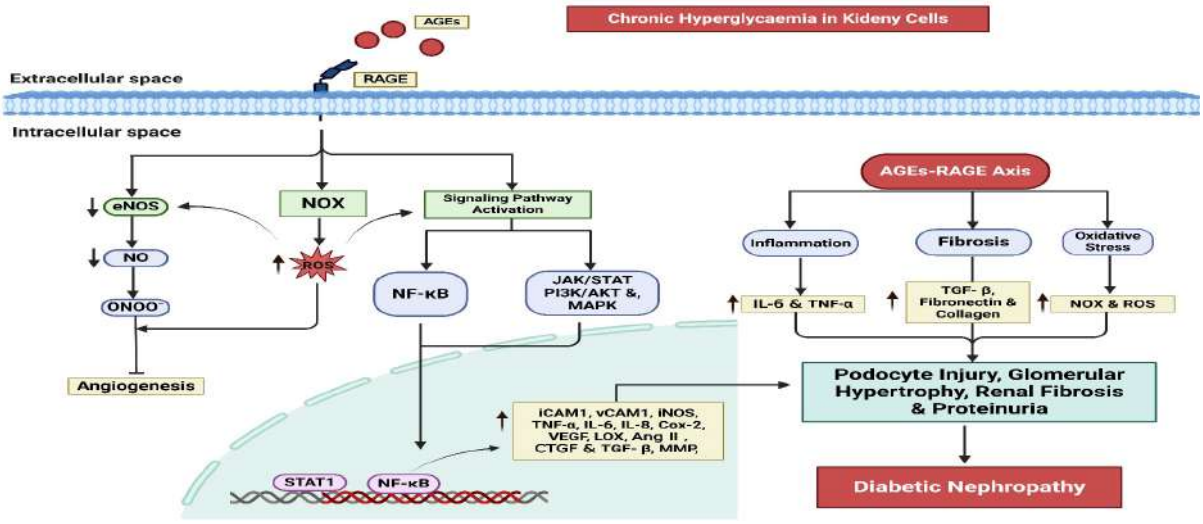

Figure 3: RAGE Pathway involved in the development of DN

Sustained hyperglycemia increases the production of AGEs that stimulate RAGEs, leading to tubule-interstitial fibrosis, inflammation, and glomerulosclerosis. The interaction between RAGE and AGEs triggers oxidative stress, chronic inflammation, and activation of signaling pathways in renal tissues, contributing to the development of glomerulosclerosis (DN). NF-κB promotes the transcription of genes for pro-inflammatory cytokines and adhesion molecules, while AGEs activate Akt in renal cells, resulting in enhanced permeability of podocytes and impaired endothelial homeostasis. Jak/Stat proteins encourage heightened inflammation and cell multiplication, resulting in kidney injury. An intensified triad of oxidative stress, inflammation, and fibrosis leads to DN, with increased activities of NADPH and ROS levels, reduced antioxidant enzyme activities, and elevated proinflammatory cytokines like TNF-α and IL-6. The increased production of profibrotic cytokines, TGF-β, and extracellular fibrotic fibers, fibronectin, and collagen, contributes to the development of DN. Abbreviations: AGEs, Advanced Glycation End products; Ang II, Angiotensin II; Cox-2, Cyclooxygenase 2; CTGF, Connective Tissue Growth Factor; eNOS, Endothelial Nitric Oxide Synthase; ICAM-1, Intercellular Adhesion Molecule 1; IL-6, Interleukin 6; IL-8, Interleukin 8; iNOS, Inducible Nitric Oxide Synthase; JAK/STAT, Janus Kinase/Signal Transducers and Activators of Transcription; LOX, Lysyl Oxidase; MAPK, Mitogen-Activated Protein Kinase; MMP, Matrix Metalloproteinases; NF-KB, Nuclear Factor Kappa B. NO, Nitric Oxide; NOX, NADPH Oxidase; PI3K-AKT, Phosphatidyl Inositol 3-Kinase-protein kinase B; RAGE, Receptor of Advanced Glycation End product; ROS, Reactive Oxygen Species; TGF-B, Transforming Growth Factor Beta; TNF-α, Tumor Necrosis Factor Alpha; VCAM-1, Vascular Cell Adhesion Molecule 1; VEGF, Vascular Endothelial Growth Factor.

Numerous studies have suggested an association between RAGE polymorphisms and DN. *Wei Cai et al.* conducted a study on the 2184A/G polymorphism. Their research showed that the 2184A/G polymorphism in the RAGE gene was strongly associated with DN [67]. *Zhanqin Shi et al.*'s meta-analysis study showed that the -429CC genotype of the RAGE gene polymorphism could be a contributing factor to DN in individuals with T2DM [68]. Another study demonstrated that 1704G/T and 2184A/G RAGE polymorphisms are associated with the antioxidant levels in individuals with NIDDM. It is obvious that the severity of vascular complications in diabetes, such as DN, is connected to the plasma concentrations of antioxidants. It indicates that these polymorphisms could be associated with oxidative stress, and they could increase the risk of developing DN [69]. In type 1 diabetic patients with poor metabolic control, the -374T/A polymorphism is associated with DN [70,71]. *Ying Zhang et al.* conducted a case-control study and showed that the T allele of rs184003 and the C allele of rs1800625 in the RAGE gene are associated with increased risk of DN [72]. While RAGE shows potential in risk prediction and outcomes prognosis in various diseases [73], additional research is required to evaluate the role of RAGE polymorphisms in the development of DN. It has been proposed Transcription factor 7 like 2 gene polymorphism and advanced glycation end products as risk factors for DN.

Transcription factor 7-like 2

The transcription factor 7-like 2 (TCF7L2), formerly known as TCF4 or transcription factor 4, belongs to the T-cell factor/lymphoid enhancer binding factor family (TCF/LEF), which consists of transcription factors that bind to DNA via a high-mobility group (HMG) domain. It plays a role in gene activation associated with the downstream processes of the Wnt signaling pathway. The activation of Wnt target genes specifically inhibits proglucagon production in enteroendocrine cells [74,75]. The TCF7L2 gene in humans is found on chromosome 10q25.3 [76]. Proteins that participate in the Wnt network, including TCF7L2, have been associated with a range of prevalent diseases. Targeted disruption of TCF7L2 in pancreatic β cells negatively affects their secretory capabilities and reduces β cell mass [77]. Clinical research has indicated that the TCF7L2 gene negatively affects glucose tolerance by influencing both glucagon and insulin release. The TCF7L2 gene has garnered significant interest because of its strong genetic association to T2DM. Multiple studies have also determined that SNP in the TCF7L2 gene is associated with DM. It also triggers the expression of many genes that are part of the Wnt pathway, which has a considerable impact on the progression of DN [74,75,78-80]. AGEs activated TCF7L2 expression via TGF-β, which in turn could facilitate the translocation of TCF7L2 from the cytoplasm into the nucleus. Subsequently, TCF7L2 bound to the promoter of the activin

receptor-linked kinase 1 (ALK1), leading to an increase in ALK1 expression. The elevated levels of ALK1 intensified the effects of TGF-β and further stimulated the phosphorylation of Smad1. These interactions prompted phenotypic alterations in mesangial cells, ultimately contributing to the onset of glomerulosclerosis. Indeed, the AGEs/TGF-β/TCF7L2/ALK1/Smad1 signaling pathway is crucial in the progression of DN [81].

Zhenqian Fan et al. investigated a meta-analysis and showed an association between DN and TCF7L2 polymorphisms [82]. The Taiwanese population study indicated that TCF7L2 interacts with ADIPOQ (adiponectin) and growth hormone secretagogue receptor (GHS-R) in determining susceptibility to diabetic DN [83]. In Caucasian populations, the TCF7L2 rs7903146 T allele showed a strong correlation with ESRD [84]. Also, in the Indian population, the rs12255372 and rs7903147 polymorphisms of TCF7L2 are the most extensively investigated variants [85]. *Peng Xue et al.* discovered a notable association between rs7903146-T alleles and the interaction of rs7903146-T with current smoking, which contributes to a higher risk of DN [86]. An Italian study evaluated the impact of rs7903146 in the elderly population [87], and the polymorphism was associated with lower insulin levels, smaller waist sizes, and a reduced lipid risk [88]. *Gambino et al.* investigated the relationship between the rs7903146 SNP and metabolic variables both at baseline and after 6 years of follow-up, discovering a correlation between the T allele and hyperglycemia and B-cell dysfunction [89]. Another study indicated that TCF7L2 gene variants rs7903146 and rs290487 were associated with DN and both hypertension and dyslipidemia in individuals with T2DM [90]. The rs11196218 genotype and allele frequency distribution in TCF7L2 differed significantly between DN and non-DN patients in the Chinese population, implying a role for TCF7L2 in diabetes development [91]. Although TCF7L2 demonstrates promise in predicting risks and prognosing outcomes across different diseases, further investigation is required to evaluate the influence of TCF7L2 SNP on the onset of DN.

Limitations

The etiology of DN is complicated and multifactorial. Our study did not evaluate the correlations between SNPs related to glucose metabolism and other risk factors, including environmental variables, racial disparities, and ethnic confounders. Also, due to the type of narrative review study, some glucose metabolism-related gene polymorphisms, were not analyzed in our study. The current research indicates that glucose metabolism-related genes can predict the development of DN. These variations should be utilized to create predictive models for future DN occurrences in different populations. GWAS, association studies, meta-analysis, and cohort studies in polymorphisms of glucose metabolism-related genes are proposed in order to achieve more definitive results.

Conclusion

DN is increasingly posing a significant challenge for the healthcare system, as many aspects of it remain poorly understood. It is a diverse and complex disease influenced by multiple genes, proteins, and environmental factors that contribute to its risk. Given the increasing impact of the disease on individuals with diabetes, it is crucial to recognize predictors of DN to effectively manage this condition. The development of DN has been significantly influenced by genetic predisposition. The onset and progression of DN are influenced by a multitude of genes, with various allelic polymorphisms showing measurable impacts on the disease's progression, thus increasing the overall risk. Genes related to glucose metabolism are the most important factors in the progression of the disease. Integrating different studies on gene polymorphisms associated with DN with the latest advancements in human bioinformatics, proteomics and genomics, could enhance prevention, early diagnosis and treatment by providing a deeper understanding of the disease's pathogenesis. To our knowledge, this is the first report of genes involved in glucose metabolism associated with DN, and it may serve as a significant resource for pinpointing individuals at risk of developing DN in the future. In this review, global research initiatives have focused on pinpointing the susceptibility gene involved in glucose metabolism associated with DN. Incorporating genetic research into the design and analysis of drug trials may result in the creation of genetic biomarkers that can forecast treatment responses.

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Data Availability

Not applicable

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Author Contributions Statement

The concept, design, and final approval of the manuscript for publication were done by M.M., H.R., G.K., and H.M. Preparation of work for submission by critically revising for important intellectual content was done by H.R. and H.M. Also, M.M., M.K., and S.D. wrote the main manuscript text. M.M., and S.B.D designed the figures and tables. The final manuscript was read and approved by all authors, who have agreed to be responsible for all aspects of the work and to ensure that any questions regarding the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Conflict of Interest

No potential conflict of interest was reported by the authors.

References

1. Matoori S (2022) Diabetes and its Complications. ACS Publications; 513-5.

2. Whiting DR, Guariguata L, Weil C, Shaw J (2011) IDF diabetes atlas: global estimates of the prevalence of diabetes for 2011 and 2030. Diabetes research and clinical practice. 94: 311-21.

3. Van Dril E, Schumacher P (2022) Chronic Kidney Disease in Patients with Diabetes. Kidney. 45: S1-264.

4. Ghaderian SB, Hayati F, Shayanpour S, Mousavi SSB (2015) Diabetes and end-stage renal disease; a review article on new concepts. Journal of renal injury prevention. 4: 28.

5. Bikbov B, Purcell CA, Levey AS, Smith M, Abdoli A, Abebe M, et al. (2020) Global, regional, and national burden of chronic kidney disease, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. The Lancet. 395: 709–33.

6. Trivedi N, Sodani P (2024) A Study on the Economic Evaluation of End-stage Renal Disease Treatment: Kidney Transplantation Versus Haemodialysis. Journal of Health Management. 26: 284–92.

7. Wu T, Ding L, Andoh V, Zhang J, Chen L (2023) The mechanism of hyperglycemia-induced renal cell injury in diabetic nephropathy disease: An update. Life. 13: 539.

8. Donate-Correa J, Martín-Núñez E, Muros-de-Fuentes M, Mora-Fernández C, Navarro-González JF (2015) Inflammatory cytokines in diabetic nephropathy. Journal of Diabetes Research. 2015: 1–10.

9. Kriz W, Löwen J, Gröne H-J (2023) The complex pathology of diabetic nephropathy in humans. Nephrology Dialysis Transplantation. 38: 2109–19.

10. Selby NM, Taal MW (2020) An updated overview of diabetic nephropathy: Diagnosis, prognosis, treatment goals and latest guidelines. Diabetes, Obesity and Metabolism. 22: 3–15.

11. Tziomalos K, Athyros VG (2015) Diabetic nephropathy: new risk factors and improvements in diagnosis. The Review of Diabetic Studies: RDS. 12: 110–8.

12. Tziastoudi M, Stefanidis I, Zintzaras E (2020) The genetic map of diabetic nephropathy: evidence from a systematic review and meta-analysis of genetic association studies. Clinical Kidney Journal. 13: 768–81.

13. Song J, Ni J, Yin X (2023) The genetic side of diabetic kidney disease: a review. International Urology and Nephrology. 55: 335–43.

14. Lindner TH, Mönks D, Wanner C, Berger M (2003) Genetic aspects of diabetic nephropathy. Kidney International. 63: S186–S191.

15. Pezzolesi MG, Krolewski AS (2019) The genetics of diabetic nephropathy. Diabetic Nephropathy: Pathophysiology and Clinical Aspects. 2019: 89–112.

16. Wei L, Xiao Y, Li L, Xiong X, Han Y, Zhu X, Sun L (2018) The susceptibility genes in diabetic nephropathy. Kidney Diseases. 4: 226–37.

17. Mooyaart AL (2014) Genetic associations in diabetic nephropathy. Clinical and Experimental Nephrology. 18: 197–200.

18. Tanzadehpanah H, Modaghegh MHS, Mahaki H (2023) Key biomarkers in cerebral arteriovenous malformations: Updated review. The Journal of Gene Medicine. 25: e3559.

19. Mahaki H, Modaghegh MHS, Isfahani ZN, Daddost RA, Molaei P, Ahmadyousefi Y, et al. (2021) The role of peptide-based tumor vaccines on cytokines of adaptive immunity: A review. International Journal of Peptide Research and Therapeutics. 27: 2527–42.

20. Modaghegh MHS, Tanzadehpanah H, Kamyar MM, Manoochehri H, Sheykhhasan M, Forouzanfar F, et al. (2024) The role of key biomarkers in lymphatic malformation: An updated review. The Journal of Gene Medicine. 26: e3665.

21. Sardarian K, Maghsood AH, Farimani M, Hajiloii M, Saidijam M, Rezaeepoor M, et al. (2018) Evaluation of Toxoplasma gondii B1 gene in placental tissues of pregnant women with acute toxoplasmosis. Advanced Biomedical Research. 7: 119.

22. Singh Grewal A, Bhardwaj S, Pandita D, Lather V, Singh Sekhon B (2016) Updates on aldose reductase inhibitors for management of diabetic complications and non-diabetic diseases. Mini Reviews in Medicinal Chemistry. 16: 120–62.

23. Gupta JK (2024) The role of aldose reductase in polyol pathway: An emerging pharmacological target in diabetic complications and associated morbidities. Current Pharmaceutical Biotechnology. 25: 1073–81.

24. Thakur S, Gupta SK, Ali V, Singh P, Verma M (2021) Aldose reductase: A cause and a potential target for the treatment of diabetic complications. Archives of Pharmacal Research. 44: 655–67.

25. Neamat-Allah M, Feeney S, Savage D, Maxwell A, Hanson R, Knowler W, et al. (2001) Analysis of the association between diabetic nephropathy and polymorphisms in the aldose reductase gene in type 1 and type 2 diabetes mellitus. Diabetic Medicine. 18: 906–14.

26. Demaine A (2003) Polymorphisms of the aldose reductase gene and susceptibility to diabetic microvascular complications. Current Medicinal Chemistry. 10: 1389–98.

27. Ko GT, Chow C, Li C, Yeung VT, Cockram CS (1995) Insulin-dependent diabetes mellitus presenting as diabetic ketoacidosis in pregnancy. Australian and New Zealand Journal of Obstetrics and Gynaecology. 35: 321–2.

28. Liu Y, Wat N, Chung S, Ko B, Lam K (2002) Diabetic nephropathy is associated with the 5′end dinucleotide repeat polymorphism of the aldose reductase gene in Chinese subjects with type 2 diabetes. Diabetic Medicine. 19: 113-8.

29. Zhao HL, Tong PC, Lai FM, Tomlinson B, Chan JC (2004) Association of glomerulopathy with the 5′end polymorphism of the aldose reductase gene and renal insufficiency in type 2 diabetic patients. Diabetes. 53: 2984–91.

30. Heesom AE, Hibberd ML, Millward A, Demaine AG (1997) Polymorphism in the 5′end of the aldose reductase gene is strongly associated with the development of diabetic nephropathy in type 1 diabetes. Diabetes. 46: 287–91.

31. Gosek K, Moczulski D, Zukowska-Szczechowska E, Grzeszczak W (2005) C-106T polymorphism in promoter of aldose reductase gene is a risk factor for diabetic nephropathy in type 2 diabetes patients with poor glycaemic control. Nephron Experimental Nephrology. 99: e63–7.

32. Katakami N, Kaneto H, Takahara M, Matsuoka T, Imamura K, Ishibashi F, et al. (2011) Aldose reductase C-106T gene polymorphism is associated with diabetic retinopathy in Japanese patients with type 2 diabetes. Diabetes Research and Clinical Practice. 92(3): e57–60.

33. Cui W, Du B, Cui Y, Kong L, Wu H, Wang Y, et al. (2015) Is rs759853 polymorphism in promoter of aldose reductase gene a risk factor for diabetic nephropathy? A meta-analysis. European Journal of Medical Research. 20: 1–10.

34. Henry DN, Busik JV, Brosius FC III, Heilig CW (1999) Glucose transporters control gene expression of aldose reductase, PKCα, and GLUT1 in mesangial cells in vitro. American Journal of Physiology-Renal Physiology. 277: F97–104.

35. Mueckler M, Caruso C, Baldwin SA, Panico M, Blench I, Morris HR, et al. (1985) Sequence and structure of a human glucose transporter. Science. 229: 941–5.

36. Uldry M, Thorens B (2004) The SLC2 family of facilitated hexose and polyol transporters. Pflügers Archiv. 447: 480–9.

37. Brosius FC, Heilig CW (2005) Glucose transporters in diabetic nephropathy. Pediatric Nephrology. 20: 447–51.

38. Gambaro G, Ceol M, Prete DD, D'Angelo A (2000) GLUT-1 and TGF-β: The link between hyperglycaemia and diabetic nephropathy. Nephrology Dialysis Transplantation. 15: 1476–7.

39. Lal S, Mistry K (2017) Glucose transporter 1 (GLUT1) gene frequency distribution of XbaI G>T and HaeIII T>C polymorphisms among different West Indian patients with type 2 diabetes mellitus. Gene Reports. 6: 36–40.

40. Ng DP, Canani L, Araki S, Smiles A, Moczulski D, Warram JH, Krolewski AS (2002) Minor effect of GLUT1 polymorphisms on susceptibility to diabetic nephropathy in type 1 diabetes. Diabetes. 51: 2264–69.

41. Cui W, Du B, Zhou W, Jia Y, Sun G, Sun J, et al. (2012) Relationship between five GLUT1 gene single nucleotide polymorphisms and diabetic nephropathy: a systematic review and meta-analysis. Molecular Biology Reports; 39: 8551–8.

42. Zintzaras E, Stefanidis I (2005) Association between the GLUT1 gene polymorphism and the development of diabetic nephropathy: a meta-analysis. Journal of Human Genetics; 50: 602–10.

43. Hodgkinson A, Page T, Millward B, Demaine A (2005) A novel polymorphism in the 5flanking region of the glucose transporter (GLUT1) gene is strongly associated with diabetic nephropathy in patients with Type 1 diabetes mellitus. Journal of Diabetes and its Complications. 19: 65-9.

44. Makni K, Jarraya F, Rebai M, Mnif F, Boudawara M, Hamza N, et al. (2008) Risk genotypes and haplotypes of the GLUT1 gene for type 2 diabetic nephropathy in the Tunisian population. Annals of human biology. 35: 490-8.

45. Amini S, Javanmardi M, Mokarizadeh A, Maroofi F, Jalali C, Azadi NA, et al. (2016) Association of HaeIII single nucleotide polymorphisms in the SLC2A1 gene with risk of diabetic nephropathy; evidence from Kurdish patients with type 2 diabetes mellitus. QJM: An International Journal of Medicine. 109: 399-404.

46. Tarnow L, Grarup N, Hansen T, Parving HH, Pedersen O (2001) Diabetic microvascular complications are not associated with two polymorphisms in the GLUT-1 and PC-1 genes regulating glucose metabolism in Caucasian type 1 diabetic patients. Nephrology Dialysis Transplantation. 16: 1653-6.

47. Grzeszczak W, Moczulski DK, Zychma M, Zukowska-Szczechowska E, Trautsolt W, Szydlowska I (2001) Role of GLUT1 gene in susceptibility to diabetic nephropathy in type 2 diabetes. Kidney international. 59: 631-6.

48. Marques T, Patente T, Monteiro M, Cavaleiro A, Queiroz M, Nery M, et al. (2015) Association of single nucleotide polymorphisms in the gene encoding GLUT1 and diabetic nephropathy in Brazilian patients with type 1 diabetes mellitus. Clinica Chimica Acta. 444: 170-5.

49. Kulin A, Kucsma N, Bohár B, Literáti-Nagy B, Korányi L, Cserepes J, et al. (2022) Genetic modulation of the GLUT1 transporter expression—potential relevance in complex diseases. Biology. 11: 1669.

50. Sharma P, Singh S, Sharma N, Singla D, Guarve K, Grewal AS (2022) Targeting human Glucokinase for the treatment of type 2 diabetes: an overview of allosteric Glucokinase activators. Journal of Diabetes & Metabolic Disorders. 21: 1129-37.

51. She L, Li W, Guo Y, Zhou J, Liu J, Zheng W, et al. (2022) Association of glucokinase gene and glucokinase regulatory protein gene polymorphisms with gestational diabetes mellitus: A case–control study. Gene. 824: 146378.

52. Iwata M, Maeda S, Kamura Y, Takano A, Kato H, Murakami S, et al. (2012) Genetic risk score constructed using 14 susceptibility alleles for type 2 diabetes is associated with the early onset of diabetes and may predict the future requirement of insulin injections among Japanese individuals. Diabetes care. 35: 1763-70.

53. Köttgen A, Pattaro C, Böger CA, Fuchsberger C, Olden M, Glazer NL, et al. (2010) New loci associated with kidney function and chronic kidney disease. Nature genetics. 42: 376-84.

54. Deshmukh H, Palmer C, Morris A, Colhoun H (2013) Investigation of known estimated glomerular filtration rate loci in patients with type 2 diabetes. Diabetic medicine. 30: 1230-5.

55. Yan D, Wang J, Jiang F, Zhang R, Sun X, Wang T, et al. (2016) Association between serum uric acid related genetic loci and diabetic kidney disease in the Chinese type 2 diabetes patients. Journal of Diabetes and its Complications. 30: 798-802.

56. Liu Y-Y, Wan Q (2023) Relationship between GCKR gene rs780094 polymorphism and type 2 diabetes with albuminuria. World Journal of Diabetes. 14: 1803.

57. Wang K, Shi M, Yang A, Fan B, Tam CH, Lau E, et al. (2022) GCKR and GCK polymorphisms are associated with increased risk of end-stage kidney disease in Chinese patients with type 2 diabetes: The Hong Kong Diabetes Register

(1995–2019). Diabetes Research and Clinical Practice. 193: 110118.

58. Al Madhoun A (2024) Glucokinase regulatory protein rs780094 polymorphism is associated with type 2 diabetes mellitus, dyslipidemia, non-alcoholic fatty liver disease, and nephropathy. World Journal of Diabetes. 15: 814.

59. Jung H, Joo J, Jeon Y, Lee J, In J, Kim D, et al. (2011) Advanced glycation end products downregulate glucokinase in mice. Diabetes/Metabolism Research and Reviews. 27: 557-63.

60. Mosquera-Sulbarán JA, Hernández-Fonseca JP (2022) Advanced Glycation End Products in Diabetes. Biomarkers in Diabetes: Springer; 171-94.

61. Wu XQ, Zhang DD, Wang YN, Tan YQ, Yu XY, Zhao YY (2021) AGE/RAGE in diabetic kidney disease and ageing kidney. Free Radical Biology and Medicine. 171: 260-71.

62. Egaña-Gorroño L, López-Díez R, Yepuri G, Ramirez LS, Reverdatto S, Gugger PF, et al. (2020) Receptor for advanced glycation end products (RAGE) and mechanisms and therapeutic opportunities in diabetes and cardiovascular disease: insights from human subjects and animal models. Frontiers in cardiovascular medicine. 7: 37.

63. Chawla D, Tripathi AK (2019) Role of advanced glycation end products (AGEs) and its receptor (RAGE)-mediated diabetic vascular complications. Integr Food Nutr Metab. 6: 1-6.

64. Perrone A, Giovino A, Benny J, Martinelli F (2020) Advanced glycation end products (AGEs): biochemistry, signaling, analytical methods, and epigenetic effects. Oxidative medicine and cellular longevity. 2020: 3818196.

65. Taguchi K, Fukami K (2023) RAGE signaling regulates the progression of diabetic complications. Frontiers in Pharmacology. 14: 1128872.

66. Xiong F, Leonov S, Howard AC, Xiong S, Zhang B, Mei L, et al. (2011) Receptor for advanced glycation end products (RAGE) prevents endothelial cell membrane resealing and regulates F-actin remodeling in a β-catenin-dependent manner. Journal of Biological Chemistry. 286: 35061-70.

67. Cai W, Li J, Xu J-X, Liu Y, Zhang W, Xiao J-R, et al. (2015) Association of 2184AG polymorphism in the RAGE gene with diabetic nephropathy in Chinese patients with type 2 diabetes. Journal of diabetes research. 2015: 310237.

68. Shi Z, Lu W, Xie G (2015) Association between the RAGE gene-374T/A,-429T/C polymorphisms and diabetic nephropathy: a meta-analysis. Renal Failure. 37: 751-6.

69. Mu J, Stejskalov A (2001) Polymorphisms 1704G/T and 2184A/G in the RAGE gene are associated with antioxidant status. Metabolism-Clinical and Experimental. 50: 1152-60.

70. Pettersson-Fernholm K, Forsblom C, Hudson BI, Perola M, Grant PJ, Groop P-H, Group FS (2003) The functional– 374 T/A RAGE gene polymorphism is associated with proteinuria and cardiovascular disease in type 1 diabetic patients. Diabetes. 52: 891-4.

71. Abdel-Azeez HA, El-Okely AM (2009) Association of the receptor for advanced glycation end products (RAGE)-374 T/A gene polymorphism and circulating soluble RAGE with nephropathy in type 1 diabetic patients. The Egyptian Journal of Immunology. 16: 95-106.

72. Zhang Y, Jia N, Hu F, Fan N, Guo X, Du H, et al. (2017) Association of single-nucleotide polymorphisms in the RAGE gene and its gene-environment interactions with diabetic nephropathy in Chinese patients with type 2 diabetes. Oncotarget. 8: 96885.

73. Sardarian K, Maghsood AH, Farimani M, Hajiloii M, Saidijam M, Farahpour M, et al. (2019) Detection of Toxoplasma gondii B1 gene in placenta does not prove congenital toxoplasmosis. Human Antibodies. 27: 31-5.

74. Grant SF, Thorleifsson G, Reynisdottir I, Benediktsson R, Manolescu A, Sainz J, et al. (2006) Variant of transcription factor 7-like 2 (TCF7L2) gene confers risk of type 2 diabetes. Nature genetics. 38: 320-3.

75. Sladek R, Rocheleau G, Rung J, Dina C, Shen L, Serre D, et al. (2007) A genome-wide association study identifies novel risk loci for type 2 diabetes. Nature. 445: 881-5.

76. Duval A, Busson-Leconiat M, Berger R, Hamelin R (2000) Assignment1 of the TCF-4 gene (TCF7L2) to human

chromosome band 10q25. 3. Cytogenetic and Genome Research. 88: 264-5.

77. Duval A, Rolland S, Tubacher E, Bui H, Thomas G, Hamelin R (2000) The human T-cell transcription factor-4 gene: structure, extensive characterization of alternative splicings, and mutational analysis in colorectal cancer cell lines. Cancer research. 60: 3872-9.

78. van Amerongen R, Nusse R (2009) Towards an integrated view of Wnt signaling in development. Development. 136: 3205-14.

79. Lucero OM, Dawson DW, Moon RT, Chien AJ (2010) A re-evaluation of the "oncogenic" nature of Wnt/β--catenin signaling in melanoma and other cancers. Current oncology reports. 12: 314-8.

80. Wenzel J, Rose K, Haghighi EB, Lamprecht C, Rauen G, Freihen V, et al. (2020) Loss of the nuclear Wnt pathway effector TCF7L2 promotes migration and invasion of human colorectal cancer cells. Oncogene. 39: 3893-909.

81. Araoka T, Abe H, Tominaga T, Mima A, Matsubara T, Murakami T, et al. (2010) Transcription factor 7-like 2 (TCF7L2) regulates activin receptor-like kinase 1 (ALK1)/Smad1 pathway for development of diabetic nephropathy. Molecules and cells. 30: 209-18.

82. Ning B, Wang J, Li B, Lyu C (2022) Association of the transcription factor 7-Like 2 (TCF7L2) rs7903146 polymorphism with the risk of diabetic nephropathy: a meta-analysis. Hormone and Metabolic Research. 54: 472-80.

83. Wu LSH, Hsieh CH, Pei D, Hung YJ, Kuo SW, Lin E (2009) Association and interaction analyses of genetic variants in ADIPOQ, ENPP1, GHSR, PPARγ and TCF7L2 genes for diabetic nephropathy in a Taiwanese population with type 2 diabetes. Nephrology Dialysis Transplantation. 24: 3360-6.

84. Buraczynska M, Zukowski P, Ksiazek P, Kuczmaszewska A, Janicka J, Zaluska W (2014) Transcription factor 7-like 2 (TCF7L2) gene polymorphism and clinical phenotype in end-stage renal disease patients. Molecular biology reports. 41: 4063-8.

85. Bodhini D, Radha V, Dhar M, Narayani N, Mohan V (2007) The rs12255372 (G/T) and rs7903146 (C/T) polymorphisms of the TCF7L2 gene are associated with type 2 diabetes mellitus in Asian Indians. Metabolism. 56: 1174-8.

86. Xue P, Cao H, Ma Z, Zhou Y, Wang N (2021) Transcription factor 7-like 2 gene-smoking interaction on the risk of diabetic nephropathy in Chinese Han population. Genes and Environment. 43: 1-6.

87. Gambino R, Bo S, Gentile L, Musso G, Pagano G, Cavallo-Perin P, Cassader M (2010) Transcription factor 7-like 2 (TCF7L2) polymorphism and hyperglycemia in an adult Italian population-based cohort. Diabetes Care. 33: 1233-5.

88. Melzer D, Murray A, Hurst AJ, Weedon MN, Bandinelli S, Corsi AM, et al. (2006) Effects of the diabetes linked TCF7L2 polymorphism in a representative older population. BMC medicine. 4: 1-8.

89. Bonetti S, Trombetta M, Malerba G, Boselli L, Trabetti E, Muggeo M, et al. (2011) Variants and haplotypes of TCF7L2 are associated with β-cell function in patients with newly diagnosed type 2 diabetes: the Verona Newly Diagnosed Type 2 Diabetes Study (VNDS) 1. The Journal of Clinical Endocrinology & Metabolism. 96: E389-93.

90. Abbas SAN, Raza ST, Mir SS, Siddiqi Z, Zaidi A, Zaidi Z, Mahdi F (2019) Association of variants rs7903146 and rs290487 of TCF7L2 gene with diabetic nephropathy and co--morbidities (hypertension and dyslipidemia) in type 2 diabetes mellitus. Meta Gene. 20: 100561.

91. Fu L, Lin Y, Yang Z, Yin Y (2012) Association analysis of genetic polymorphisms of TCF7L2, CDKAL1, SLC30A8, HHEX genes and microvascular complications of type 2 diabetes mellitus. Zhonghua yi xue yi Chuan xue za zhi= Zhonghua Yixue Yichuanxue Zazhi= Chinese Journal of Medical Genetics. 29: 194-9.

92. Dieter C, Lemos NE, Corrêa NRdF, Pellenz FM, Canani LH, Crispim D, Bauer AC (2022) The A allele of the rs759853 single nucleotide polymorphism in the AKR1B1 gene confers risk for diabetic kidney disease in patients with type 2 diabetes from a Brazilian population. Archives of Endocrinology and Metabolism. 66: 12-8.

93. Xu M, Chen X, Yan L, Cheng H, Chen W (2008) As-

sociation between (AC) n dinucleotide repeat polymorphism at the 5'-end of the aldose reductase gene and diabetic nephropathy: a meta-analysis. Journal of molecular endocrinology. 40: 243-51.

94. Stefanidis I, Tziastoudi M, Tsironi E, Dardiotis E, Tachmitzi S, Fotiadou A, et al. (2018) The contribution of genetic variants of SLC2A1 gene in T2DM and T2DM-nephropathy: association study and meta-analysis. Renal failure. 40: 561-76.

95. Matsunaga-Irie S, Maruyama T, Yamamoto Y, Motohashi Y, Hirose H, Shimada A, et al. (2004) Relation between development of nephropathy and the p22phox C242T and receptor for advanced glycation end product G1704T gene polymorphisms in type 2 diabetic patients. Diabetes care. 27: 303-7.

96. Jiang GT, Chen LJ, Bai QM, Jiao JD, Shi WW (2016) Association between RAGE gene polymorphisms and the susceptibility of diabetic nephropathy. Int J Clin exp pathol. 9: 2271-6.

97. Morgan MF, Salam RF, Rady NH, Alnaggar ARL, Ammar SH, Ghanem NS (2020) The association of transcription factor 7 like 2 gene polymorphism with diabetic nephropathy in patients with type 2 diabetes mellitus. Current Diabetes Reviews. 16: 370-5.

98. Alami FM, Ahmadi M, Bazrafshan H, Tabarraei A, Khosravi A, Tabatabaiefar MA, Samaei NM (2012) Association of the TCF7L2 rs12255372 (G/T) variant with type 2 diabetes mellitus in an Iranian population. Genetics and Molecular Biology. 35: 413-7.

99. Hussain H, Ramachandran V, Ravi S, Sajan T, Ehambaram K, Gurramkonda VB, et al. (2014) TCF7L2 rs7903146 polymorphism and diabetic nephropathy association is not independent of type 2 diabetes—a study in a south Indian population and meta-analysis. Endokrynologia Polska. 65: 298-305.