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REVIEW

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Effect of oxidative stress-related genetic variants: "Explicating the role of reactive oxygen species influenced antioxidant gene polymorphism," a risk stratification of type 2 diabetes mellitus-associated nephropathy: a systematic review

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Abstract

Type 2 diabetes mellitus is believed to be associated with microvascular complications which include diabetic retinopathy, nephropathy, and neuropathy. Oxidative stress plays a predominant role in the pathogenesis of DN and also influences metabolic endeavor and its hemodynamic pathways to possess various associations with renal complications, and one such is diabetic nephropathy which is the insignificant cause of end-stage renal disease. Renal injury in DN is predominantly related to the inclined oxidative stress, with influential metabolic endeavor and its hemodynamic pathways. Hyperglycemia, an hallmark feature of diabetes, promotes conditions of the diabetic patients responsible for higher reactive oxygen species production, which ultimately leads to increased oxidative stress, and this is considered to be the important event in the initiation of DN. Pertaining to oxidative stress, ROS is generated mostly by the variety of important pathways, in which this paves the way for antioxidant therapeutic approach preventing the initiation and progression/aggravation of tubular injury in DN. The most salient antioxidant enzymes including superoxide dismutase, catalase, glutathione-S-transferase, and glutathione peroxidase are considered as prime elements involved in the assembly and discharge of reactive metabolites. Therefore, this review highlights that antioxidant gene polymorphisms also postulate that this in these antioxidant genes may be a major cause for the pathogenesis of DN. Hence, it could also answer many questions put forth by researchers, and clinicians detecting the single-nucleotide polymorphism of these antioxidant genes and targeting therapeutic approach can enhance the genetic changes and help to reduce severity at the early stages of DN. Additionally, this literature review also shows the importance of regional population studies on detecting the SNPs of antioxidant gene which in turn reflects the status of oxidative stress involved in the pathogenesis of DN associated with T2D.

Keywords Type 2 diabetes, Diabetic nephropathy, SOD, CAT, GST, GPx, SNP

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Background

Diabetic nephropathy (DN) is one of the most worldwide public health issues associated with severe complications and growing mortality. Reactive oxygen species (ROS) mimics a crucial role in pathogenesis of DN when its levels are elevated in the intracellular membrane. This leads

to the formation of oxidized lipids, DNA, and proteins, subsidizing to cellular damage [1]. There are various evidences showing a drastic response for obese people following a calorie restricted program which could alter a person's body composition, peripheral lipid content, blood pressure, and insulin resistance depending on their genetic profile and various single-nucleotide polymorphisms (SNPs). Apparently, SNPs involving antioxidant enzymes such as catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GPx) have been sorted in coding and untranslated regions influencing the enzyme action. These enzymes are the important factors to resist the occurrence of oxidative stress by halting the initiation and circulation of innate free radicals formed during metabolism [2]. It has been revealed that these antioxidant enzymes' SNPs majorly emulate in the etiology of diabetes and its consequences, where GSTM1, GSTT1, and GSTP1 are the most significant genes in this group that are considered as a higher risk of type 2 diabetes (T2D) [3]. In western province regions, this group of antioxidant defense enzymes showing their effect to disease susceptibility is mostly age and gender specific [4, 5]. Also in Iran, some studies revealed that null alleles of GSTM1 and T1 are predicted to be the risk factors for chronic kidney disease (CKD) subjected to higher oxidative stress as a result of increased malondialdehyde (MDA) levels [6]. A study in the northern region of India has revealed the effect of gene polymorphism on GST family more prevalent for developing T2D [7]. Basic evidences provide the control of cryoprotective processes in mammals that are reflected by nuclear factor erythroid 2-related factor 2 (Nrf2) and Keap1 (Kelch-like ECH-associated protein 1, also known as inhibitor of Nrf2 (iNrf2). This particular study has emphasized the critical mechanisms by which the Keap1-Nrf2 pathway is regulated and its function in preventing acute renal injury [8].

Reactive oxygen species

A plethora of research evidences has spotted the overproduction of ROS as one of the key factors in the evolution of diabetes and diabetic vascular problems. At present, it is now understood that hyperglycemia acts as a contributing factor for the primary cause of the excess ROS generation in diabetes and that many different cell types, including endothelium, vascular smooth muscle, mesangial, and tubular epithelial cells, are capable of synthesizing ROS in a hyperglycemic environment [9]. The ROS and nitrogen species (NS) are the by-products of diabetic milieu coinciding with the pathogenesis of diabetic nephropathy conditions. But they failed to exhibit the renoprotective property of antioxidant therapy [10]. The pathophysiology of late diabetes problems is thought to be heavily influenced by ROS, which have the chemically reactive ability to directly oxidize and destroy DNA, protein, lipid, and carbohydrates. ROS-mediated hyperglycemia is associated with activation of transcription factors and a signal transduction cascade, which is a major cause of profibrotic gene transcription. There are also huge amount of studies to conceal the production of ROS [11] (Fig. 1). Moreover, enormous studies have shown that activation of apoptosis is induced by overproduction of mitochondrial ROS (mtROS) and tubular injury achieved by high-glucose ambience. This depicts the crucial role of mtROS in tubular damage, leading to DN condition [12]. Additionally, the elucidation of precise mechanism with respect to effect of ROS on tubular injury in DN demonstrates the release of signals by regulated mitochondria and aging-induced inflammatory response promotes lower ROS generation or greater antioxidant ability [13]. The progression and onset of DN are significantly influenced by intrarenal oxidative stress. ROS is overproduced when there are not enough antioxidant mechanisms present at the same time, leading to increased oxidative stress. Diabetes causes renal ROS generation to be primarily mediated by different NADPH oxidases (NOXs), but mitochondrial dysfunction and a compromised antioxidant system may also be involved [14]. There are effective elements targeting the origin of ROS production which withstands the ability to protect the kidney from oxidative injury and prevents successive development of DN. Under physiological circumstances, ROS acts as a key element in cell signaling related to renal cells' immunological defense, differentiation, endothelial cell damage, proliferation, and death [15]. However, under pathological conditions, such as in diabetes, an excess of ROS in the kidney is linked to renal inflammation, which compromises renal structure and function and eventually results in ESRD. Numerous inflammatory cells are drawn and produced inflammatory cytokines, growth factors, and transcription factors that are linked to the pathogenicity processes of DN progression by hyperglycemia-induced ROS generation [16] (Fig. 1).

Antioxidant genes involved in oxidative stress

The cell usually subsists with ROS, and oxidative stress is along the perpetuation of antioxidant enzymes that are restorative and heat-shock proteins. The overexpression of these enzymes is triggered by providing various molecular therapies to enhance and reimpose various pathological conditions [17]. Antioxidants are spontaneous nutrients that counteract with ROS and suppress the cell damage caused by oxidative stress in diabetic patients [18]. Based on the genetic possibility, the diabetic prevalence and fluctuating changes for

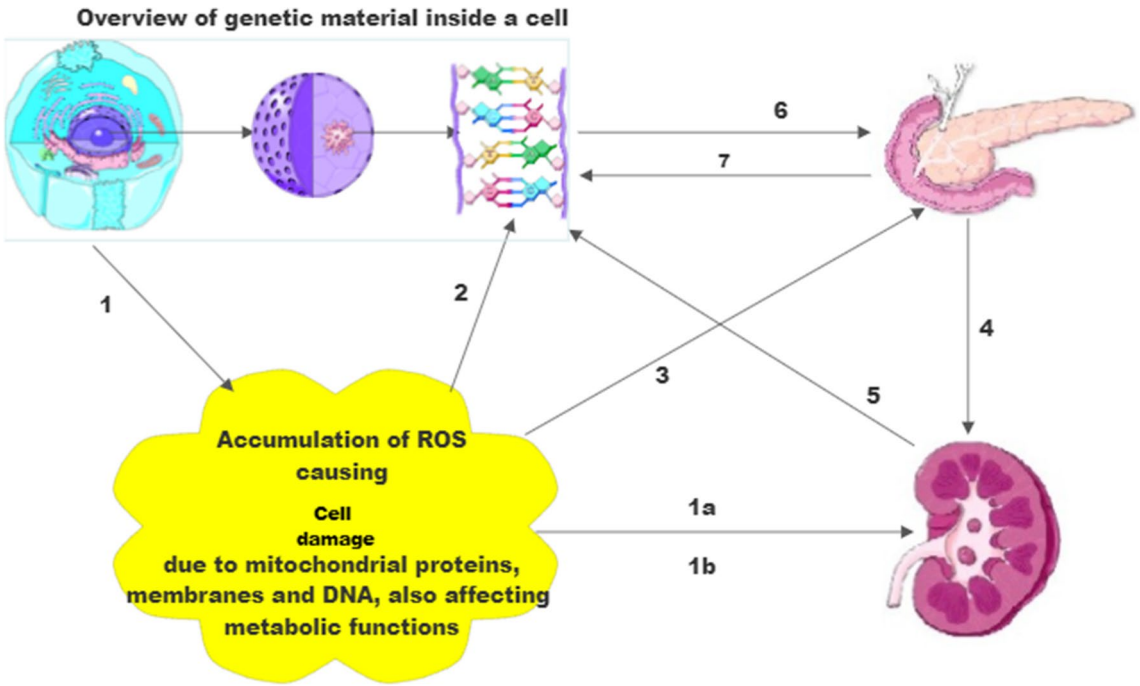

Fig. 1 Schematic representation of antioxidant gene polymorphism in the oxidative stress-induced diabetic nephropathy. 1. Mechanism of oxidative stress a. kidney injury and b. antioxidants (SOD, CAT, GST, and GPx) depletion. 2. Lifestyle modification-induced oxidative stress stimulates gene polymorphism. 3. Oxidative stress stimulates insulin resistance. 4. Insulin resistance causes T2D complication like CKD. 5. Kidney injury biomarkers stimulate antioxidant gene polymorphism. 6. Inherited genetic variant can express and leads to hyperglycemia. 7. ROS-mediated hyperglycemia in turn causes antioxidant gene polymorphism

renal disease with familial DN are varied on the basis of region. Four pathway analyses are put forth with clinical as well as experimental manifestation involved in progression of diabetes-associated microvascular complications. The pathways including polyol, advanced glycation end products, protein kinase C, and hexosamine are involved and initiated by chronic hyperglycemia. In addition, various genes have been recognized that are involved in detoxification or reduction in the generation of free radicals. There are a limited number of studies on the relationships between SOD2, glutathione-S-transferase (GSTT1), GSTP1 and GSTM1 (antioxidative xenobiotic enzymes [19]), nicotinamide adenine dinucleotide phosphate reduced (NADPH) among T2D with DN. Studies have shown the importance of restrictions fragment length polymorphism analysis (RFLP) performed on 26 polymorphisms from more than 10 genes in the oxidative stress pathway. The genes considered were superoxide dismutases (SOD1, 2, 3), endothelial nitric oxide synthase (NOS3), glutathione-S-transferases (GST) (M1, T1, and P1), and vascular endothelial growth factor (VEGF), and their associations were examined with CRI using $\chi 2$ test [20].

Superoxide dismutase (SOD)

There are three SOD isoforms seen in mammals: extracellular CuZnSOD (SOD1), cytoplasmic MnSOD (SOD2), and mitochondrial MnSOD (SOD3) [21]. Each of these SOD isoforms comes from a different gene, but they all catalyze the identical reaction to create H_2O_2 from $O_2^{\bullet -}$. Moreover, SOD is the class of metalloenzymes which are capable of having essential therapeutic properties against wide range of diseases [22]. CuZnSOD and MnSOD gene polymorphisms have been related to human DN risk in recent studies. It has also been demonstrated from the previous studies that transgenic mice carrying the SOD (SOD1 or SOD2) gene are repellent to vascular complications brought on by DN. Consequently, these results point to a crucial involvement for the SOD enzyme in the pathogenesis of DN. Conversely, the importance of the alterations in DN-associated changes in SOD enzymes is obscured [23]. The SOD2 gene is located on the chromosome 6q25.3, which expresses manganese superoxide dismutase (MnSOD), and is dispersed itself into the mitochondrial matrix where it effectively removes superoxide radicals. In this gene, Val–Ala substitution polymorphism in this gene influences the efficient transport of enzyme into the mitochondria and modifies the

antioxidant defense mechanism [24]. Moreover, some studies are related to a higher risk of developing DN associated in smoking individual, which is enhanced by the free radicals present in cigarette smoke to uplift the need for antioxidants. The progression of diabetes-associated microvascular complications may depend on the balance between genetically determined antioxidant systems and the ROS generation that is prompted brought on by smoking and hyperglycemia. Few studies have revealed the influential investigation of SOD2 rs4880 polymorphism about the risk and effect of DN and in association with smoking [25].

Catalase (CAT)

The antioxidant enzyme catalase consists of CAT gene located on the chromosome 11p13 which is significant in the kidney and crucial for the oxidative regulation in the kidney. It is an A ubiquitous enzyme catalase present in almost all aerobic organisms. The liver, kidneys, and erythrocytes have the highest concentrations because they contain the most cellular peroxisomes [26]. A key factor in the growth of oxidative stress tolerance is catalase, which mediates the formation of water and oxygen from hydrogen peroxide. It has been demonstrated that a variation in the CAT promoter affects the catalase activity in erythrocytes [27]. In recent findings, the relationship of plasma catalase activity and SNPs of CAT tag with DN is assessed with allelic variations and the abundance of DN and ESRD in diabetic patients with T1D. It was reported that lower plasma catalase activity associated with the A allele of rs7947841 was consistently linked to less favorable kidney phenotypes in three different cohorts. These findings support catalase's function in the mechanisms that protect the kidneys from oxidative stress. It was suggested that there is prerequisite of studies finding the functional CAT variations that control its allelic effects on DN will require more research [28]. Peroxisomal catalase is considered as a tetrameric hemoprotein that activates the cleavage of H_2O_2 into H_2O and O_2 [29]. Peroxisomal CAT enzyme catalyzes the breakdown of hydrogen peroxide into the less reactive components such as oxygen and water [30]. The most commonly investigated SNP in proportion to various types of diabetes (especially T2D) is 262C/T SNP (rs1049982). It has been reported that type II DM patients with the catalase genotype CT + TT had higher blood catalase activity. The CAT gene, which is found on chromosome 11, has an exon 9-262C/T polymorphism that has been linked to diabetic comorbidities such retinopathy, nephropathy, and cardiovascular disease. Additionally, in Chinese population, the CAT 262C/T polymorphism is shown to stimulate hypertriacylglycerolemia. Another study, however, found that in Caucasian patients with T2D, there were no associations reported on the CAT-262 C/T polymorphism in microvascular diabetic outcomes [31].

Glutathione-S-transferase M1 (GSTM1)

The glutathione-S-transferase family located on the human chromosome (Table 1) usually present in mammalian cytosol is categorized. Based on similarities in the amino acid sequences and patterns of subunit assembly, GSTs in the mammalian cytosol can be divided into three primary categories: alpha, mu, and pi. GST mu category is typically found to be assembled in tubuli inside the kidney. The M1, M2, M3, M4, and M5 gene loci are assumed to be the source of the human GST mu class [32]. Human GSTM1 is encoded through a polymorphic genomic locus, and its absence turned out to be linked to a homozygous deletion of the gene (null genotype) [33]. In recent studies, researchers evaluated the genetic polymorphism in T2D associated with nephropathy and those without nephropathy to see whether the GSTM1 null genotype, preventing GSTM1 from being expressed, is related to the onset of DN [34]. Genetically determined GSTM1 is one of the endogenous antioxidant enzymes which have been studied firstly to insight the acquaintance between the polymorphism in the GSTM1 gene and the onset of DN. Their findings showed that there was no statistically significant difference between the patient groups with and without nephropathy in the frequency of the GSTM1 null genotype. Finally, they proposed that the GSTM1 null genotype has no effect on the emergence of DN. The acquaintance between other genetic GST polymorphisms and DN has not yet been investigated, which suggests further research is needed to elaborate their role in the progression of DN [35].

Glutathione-S-transferase T1 (GSTT1)

A class of widely distributed and multifaceted enzymes called glutathione-S-transferases (GSTs) are assumed to guard cells from oxidative stress [36]. There are some studies proposed purpose to assess the relationship between glutathione-S-transferase (GST) gene polymorphisms and DN [37]. The odds ratio (OR) plays a major role in statistical evaluation of the data for association which was resolved using a fixed- or random-effects model [38]. It depicts that GSTM1(-) genotype (OR, 1.27; 95% CI, 1.02–1.58) and GSTT1(-)/GSTM1(-) integration (OR, 2.02; 95% CI, 1.22–3.36) are observed to significantly enhance the risk of DN, whereas the presence of Val alleles or the GSTT1(-) genotype did not appear to be associated with DN. The subgroup analytic study on Asian–Caucasian population with associated differences in DN and the GSTM1(-) was observed to be significant. This report indicates that the GSTM1(-) genotype and the combination of GSTT1(-)/GSTM1(-) are at a higher

Table 1 Overview of antioxidant gene characteristics

S.No	Gene	Cytogenetic region	SNP ID	Allelic variants	References
1	SOD isoforms				
	SOD1	21q22.11			
	SOD2	6q25.3	rs4880	A > G	[23, 25, 31, 42]
	SOD3	4p15.2			
2	CAT isoforms				
	CAT1	11p13.34	rs1049982	T > A	[28, 42]
	CAT2				
	CAT3				
3	GPx isoforms				
	GPx1	3q21.31	rs1050450	G > C	[41, 43]
	GPx2	14q23.3			
	GPx3	5q33.1			
	GPx4	19p13.3			
	GPx5	6p22.1			
	GPx6	6p22.12			
	GPx7	1p32.3			
	GPx8	5q11.2			
4	GST isoforms				
	GSTM1	1p13.3	rs35553604	C > G	[32, 33, 35, 37–39]
	GSTT1	22q11.23			
	GSTP1	11q13.12	rs1695	A > G	
5	Nrf2	2q31.2	rs6721961	T > A,C,G	[49–53]
	Nrf2-Keap1	19p13.2			

prospect of DN. Moreover, fewer studies have been reported on combined GST polymorphism compared to individual polymorphism [39]. Recent meta-analysis on GST (GSTM1, GSTT1, and GSTP1) polymorphism with coronary artery disease (CAD) depicted the combined effect of GSTM1/GSTT1 null genotypes with the highest prospect of developing diseases, which has not yet been studied so far [40].

Glutathione-S-transferase P1 (GSTP1) and glutathione peroxidase 1 (GPX1)

As they directly eliminate ROS, it is generally known that alongside SOD and CAT, GPX also constituted the striking antioxidant enzymes. Various studies have been conducted on the general functional polymorphisms in genes coding for antioxidant responsive enzymes [41]. One such study has reported that GPx1 rs1050450 (p.Pro200Leu) and SOD2 rs4880 (p.Val16Ala) SNPs have been genotyped utilizing TaqMan single-nucleotide polymorphism genotyping assays and real-time PCR systems [42]. It particularizes the observation of no association between SOD2 (rs4880), GPx1 (rs1050450), and DN ESRD due to DN in European population of Slovenia. Instead, their results support familiar polymorphisms of CAT and GSTP1 in consideration to have identified for a higher prospect of developing ESRD. Recent investigations on progression of ESRD have suggested a reduction in ESRD cases on exposure to antioxidant therapy in predialysis patients with CKD. Further assessment is required in relation to increased risk carriers of CAT and GSTP1 polymorphisms by antioxidant therapy in the prevention or at least delayed onset of ESRD [43]. Very few studies have reported GSTP1 loci in susceptibility risk of T2D, and they proved to have a significant effect which could be challenging for the future researchers to conduct large-scale cohort studies [38].

Nuclear factor of erythroid 2-related factor 2 (Nrf2)

During the onset and breakthrough of DN, oxidative stress plays a potential role, whereas nuclear factor of erythroid 2-related factor 2 (NRF2) also has a significant impact on how cells react with oxidative stress. It acts as a ubiquitous transcription factor binding with antioxidant response element (ARE) to regulate oxidative stress [44]. So, it appears that activating Nrf2 is an innovative option for the therapeutic approach to DN. The studies have conferred and outlined the curative effects of activating Nrf2 during DN condition which was observed in both primary and clinical investigations in the recent reviews [45]. It has been demonstrated that this

process depends on the nuclear factor erythroid 2-related factor 2 (Nrf2)/antioxidant responsive element (ARE) pathway. A key part of cellular resistance to oxidative stress is played by the Nrf2/ARE pathway. Phase II detoxification enzymes and antioxidants, including as heme oxygenase-1 and superoxide dismutase 1, are transcriptionally activated by Nrf2 [46]. As a result of its ability to activate antioxidant and other cytoprotective enzymes, NRF2 has so far become recognized as a viable therapeutic approach for treating a range of disorders [47]. The NRF2 gene has a few single-nucleotide polymorphisms (SNPs), including rs264723, rs13001694, rs10497511, and rs1806649 [48]. A crucial element in the positive feedback mechanism of up-regulation of the NRF2 gene to control the NRF2 protein level is thought to be carried, in specific, by SNP –617C/A (rs6721961), a NRF2 gene variable in the upstream promoter region. The risk of newly diagnosed T2D and oxidative stress has both been correlated with the rs6721961 polymorphism. However, no research has ever been conducted to determine how the polymorphism -617C/A (rs6721961) inside NRF2 affects the regulation of DN in individuals. The above-described findings on the large Chinese population have analyzed the potential relationship of the -617C/A (rs6721961) polymorphism with DN. They depicted individuals with AA carriers have been significantly associated with a declined risk of DN than those with CC carriers, regardless of reconciliation for known risk factors for DN. Anyhow, these investigators have observed that NRF2 rs6721961 polymorphism with AA homozygotes had decreased total antioxidant capacity, SOD, CAT, GST, and GPX activity with a significantly greater risk of T2D progression compared to CC homozygotes. This study conducted in the Chinese population depicted the role of NRF2 gene possessing the -617C/A (rs6721961) polymorphism which was significantly associated with DN. Hence, this review addresses the obligatory. It is concluded that additional studies are required to evaluate the influence of NRF2 gene polymorphism on oxidative stress and the risk of T2D and its comorbidities [49, 50].

Kelch-like ECH-associated protein 1 (Keap1)

Kelch-like ECH-associated protein 1 (Keap1) acts as a negative regulator of Nrf2 and fights the oxidative stress in regulating detoxification and perpetuation of homeostasis in the body [51]. The down-regulation of Nrf2 pathway was coordinated by various endogenous enzymes such as SOD, CAT, and GPX. It is widely recognized that inflammation and oxidative stress are significant factors in the development of diabetes and its consequences. In the upcoming future, targeting both of these variables using the Nrf2/Keap1 pathway might be contemplated as a unique restorative strategy [52]. Therefore, the research and advancement of numerous negligible chemical activators of the Nrf2/Keap1 pathway may yield promising outcomes in the treatment of issues related to diabetes [53]. In the recent years, research has been carried out to generate a variety of synthetic and natural compounds that can either obliquely activate the Nrf2/Keap1 pathway to provide the solicited effects. Six NRF2-ECH homology domains constitute Nrf2 (Neh). Each of these domains puts out, a unique set of activities that aid in controlling the expression of antioxidant proteins and serve as a barrier against oxidative stress imposed by trauma and infection. Also, each domain is involved in regulating the activity of Nrf2. KEAP1 is a significant regulator of the physiological regulation of Nrf2. This KEAP1 is also referred to as a Cullin 3-based E3 ligase Kelch-like ECH-associated protein 1 adaptor component. The homodimer KEAP1 is made up of the bric-a-brac (BTB), the C-terminal Kelch domain, and an intervening region (IVR) [54]. There are 27 cysteine residues in KEAP1 which function as a redox sensing mechanism for many intrinsic and extrinsic processes. Hence, this signal transduction pathway analysis paves way for researchers to conduct new findings on the polymorphisms associated with factors involved in this pathway and correlates their effect on T2D and its comorbidities. Therefore, it is clear that very little research is on progress in relation to antioxidant polymorphism involved in oxidative stress influenced during the Nrf2/Keap1 pathway which is responsible for the etiology of DN via apoptosis, proliferation, and fibrosis [55, 56].

Table 1 illustrates the gene characteristics such as their location on the respective chromosomes; SNP ID which indicates the existence of polymorphic gene variants (SOD, CAT, GPx, GST, Nrf-Keap1) in T2D-associated nephropathy; and allelic variants representing the possible base change at the relative SNP site.

Conclusion

This review addresses the significant contribution of hyperglycemia-mediated impaired antioxidants as a result of genetic predisposition, playing a pivotal role in oxidative stress-conciliated DN. Moreover, the significant regulation of these genetic factors involved in the pathogenesis of DN can be altered by maintaining adequate balance between the ROS and antioxidant levels in the individual's bloodstream. Perhaps, this review could be obliging for the researchers to investigate the interplay between genetic factors, oxidative stress, and DN to develop targeted therapeutic interventions for patients at risk. Apart from the interventional studies, there exists a wide loophole in the research involving genetic variants associated with the malfunction of signaling proteins, which in turn disrupt

the hemodynamic signaling pathways and transcription factors; consequently, triggering the production of cytokines, chemokines, and other growth factors which moderates DN, showing the importance of detecting SNPs, also concluded their detection method which is chiefly involved in sorting out numerous polymorphisms of genes associated with oxidative stress pathway. Therefore, polymerase chain reaction (PCR)-based RFLP analysis acts as a standard procedure in identification of SNPs, and SNP association with DN can be statistically evaluated. Moreover, molecular mechanisms of antioxidant genes associated with DN that are involved in oxidative stress pathway are tedious, and also, there are various loopholes to be analyzed in this area of research.

Abbreviations

T2D	Type 2 diabetes
DN	Diabetic nephropathy
ESRD	End-stage renal disease
SOD	Superoxide dismutase
MnSOD	Manganese superoxide dismutase
CAT	Catalase
GPx	Glutathione peroxidase
GST	Glutathione-S-transferase
MDA	Malondialdehyde
CKD	Chronic kidney disease
ROS	Reactive oxygen species
mtROS	Mitochondrial reactive oxygen species
NS	Nitrogen species
ARE	Antioxidant response element
NOS3	Nitric oxide synthase
VEGF	Vascular endothelial growth factor
NADPH	Nicotinamide adenine dinucleotide phosphate
NOXs	NADPH oxidases
SNP	Single-nucleotide polymorphism
RFLP	Restriction fragment length polymorphism
PCR	Polymerase chain reaction
Nrf2	Nuclear factor for erythroid 2-related factor 2
Keap1	Kelch-like ECH-associated protein 1
BTB	Bric–a-brac
IVR	Intervening region

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