REVIEW ARTICLE

Receptor for Advanced Glycation End-products (Rages) Gene Polymorphisms and Microvascular Complications in Diabetes Mellitus: A Review

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ABSTRACT

Diabetes mellitus (DM) a disorder of carbohydrates metabolism is characterized by under-utilization of glucose, which leads to persistent hyperglycaemia due to insufficient amount of insulin or existence of factors opposing insulin action. Complications of DM are acute metabolic and chronic systemic such as microvascular complications (which include nephropathy, retinopathy, neuropathy and diabetic microangiopathy). Persistent hyperglycaemia seen in DM results in increased formation of advanced glycation end-products (AGEs), which are associated with elevated oxidative stress, inflammatory responses, and eventually the emergence of complications of diabetes. AGEs interact with receptors for scavenger molecules, which remove and breakdown AGEs, and receptor for advanced glycation end-products (RAGE) to exert biological effects. Increased expression of RAGE is observed in insulin resistance DM subjects and is shown to play a role in the pathogenesis of diabetic microvascular complications. The RAGE gene, which has 11 exons and a 39 UTR, is located on chromosome 6p21.3 in the major histocompatibility complex locus in the class III area. Exons, introns, and gene regulatory areas have all been reported to have the RAGE polymorphisms. Specific RAGE gene single nucleotide polymorphisms (SNPs) is implicated in diabetic complication risks through the alteration of AGE-RAGE interaction. The RAGE gene has about 30 polymorphisms; the most often reported ones are, rs2070600, rs1800624, rs1800625, rs184003, and a 63 bp deletion are the most commonly reported. The rs2070600, rs1800625 and rs184003 were reported to be associated with microvascular complications in type 2 DM while the rs1800625 and a 63 bp deletion are associated with lower frequencies of microvascular complications in DM. This review gives detail information on receptor for advanced glycation end-products (rages) gene polymorphisms and microvascular complications in diabetes mellitus.
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Keywords: Diabetes Mellitus, Microvascular Complications, AGEs, RAGE, SNPs

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INTRODUCTION

Diabetes mellitus (DM) is a condition of carbohydrate metabolism marked by inefficient glucose usage and results in persistent hyperglycaemia due to inadequate insulin or the existence of substances interfering with insulin's action [1]. It is estimated in 2021 that 537 million people have DM Worldwide [2]. Africa accounts for about 24 million diabetic people [2]. Nigeria alone accounts for about 3.6 million patients with DM [2]. DM incidence is anticipated to rise, with a projection of 783.2 million patients worldwide; Africa`s expected projection is around 55 million by 2045 [2]. The development of DM is generally associated with the complex interactions between environmental factors and genetic conditions (including inactivity) [3]. Complications of diabetes can be grouped into two, short term and long term. The short-term complications are metabolic in nature, including hypoglycaemia, diabetic ketoacidosis (DKA), and hyperosmolar non-ketosis coma (HONK), which is now known as hyperosmolar hyperglycaemic state (HHS). While the long-term complications are systemic in nature and include both micro-vascular and macro-

vascular: Strokes, Heart attacks, and cardiovascular illnesses are among the macrovascular problems, which also include the microvascular issues including diabetic retinopathy, nephropathy, neuropathy, and diabetic microangiopathy [4].

Although glucose is the primary feature in microvascular problems found in DM, glucose action alone does not appear to be sufficient to explain the excessive atherosclerosis seen in DM participants. Chronic hyperglycaemia causes the activation of several signaling pathways, including the hexosamine pathway, the polyol pathway, the advanced-glycation end products (AGEs) pathway, Protein Kinase C (PKC), and others, which results in the overexpression of reactive oxygen species and the subsequent onset of diabetic complications [5]. Persistent high levels of blood glucose as found in DM subjects results in increased generation of AGEs, this is linked to increased oxidative stress and inflammation [5]. AGEs carry out biological functions through specific receptors. The advanced glycation end-product receptor (AGER) sometimes referred to as RAGE, is the most well-known and well-characterized receptor via which AGEs signaling occurs [6]. Increased RAGE expression is observed in disease conditions, such as DM and insulin resistance and is shown to play a critical part pathogenesis of diabetic microvascular complications [7]. Through the adjustment of numerous intracellular signaling pathways, the AGE-RAGE interaction cause changes in numerous cell functions resulting in the production of oxidative stress and target genes transcription [8]. RAGE gene is situated on chromosome 6p21.3 at the major histocompatibility complex (MHC III) locus in the class III region, the region is composed of 11 exons as well as a 39 UTR. There have been reports of RAGE polymorphisms in exons, introns, and gene regulatory regions. Some of these SNPs may have an impact on both RAGE ligand binding affinity as well as it`s transcriptional activity. Specific RAGE gene single nucleotide polymorphisms (SNPs) have been incriminated in rising risk of complications of diabetes such as nephropathy, retinopathy and cardiovascular disease, including microalbuminuria, through alterations of the AGE-RAGE interaction. Most of the RAGE SNPs reported were associated with disease onset or increased disease susceptibility [9]. Even though majority of genetic research have concentrated on the relationship existing between complications diabetes and RAGE gene polymorphisms, but knowledge about the relationship between RAGE variants and serum AGEs levels is still scarce, especially in diabetic subjects with or without difficulties [7]. About 30 polymorphisms at exons, introns, and the 65 5′-flanking regions of the RAGE gene have been discovered through genetic research [9]. In this review, we discuss an overview of RAGE gene polymorphism and its relationship with microvascular complications in diabetes mellitus.

Advanced Glycation End-Products (AGEs)-Receptor for AGEs (RAGE) Interaction

In the Human body, reducing sugars like glucose reacts non-enzymatically with proteins and nucleic acid in a process known as glycation [10, 13]. The reaction is sped-up in the presence of persistent hyperglycaemia, oxidative stress, and/or inflammatory reactions. Formation of a Schiff base between the amino group of reacting amino acid and aldehyde group of the sugar occurs at the early stage of glycation process, these undergoes a series of changes forming Amadori rearrangement products. At the earlier stages of glycation, the main products are Haemoglobin A1c (HbA1c) and glycol-albumin (glycated albumin) [10]. Protein glycation products go through an elaborate reaction process, like oxidation, dehydration, and condensation, forming dark coloured AGEs fluorescence, and molecular cross-linkages potential and other trademark features of aged tissues. AGEs are not solo chemical entities, but rather a pooled term of divergent substances sharing the above-mentioned processes and attributes [11]. The Maillard reaction, also known as glycation, is a non-enzymatic reaction that occurs when lysine side chains and N-terminal amino groups of macromolecules (proteins, phospholipids, and nucleic acids) are reduced by sugars. The resultant compounds are known as advanced glycation end products (AGEs). AGEs negatively affect the functions of proteins, lipids and DNA. Persistent hyperglycaemia hastens AGEs formation, which contributed to vascular damages seen in DM patients due to accumulation of AGEs in the extracellular matrix of vessels [4] For example one of the most common AGEs, N-(Carboxymethyl) Lysine (CML), has been linked to oxidative stress and vascular injury. The production of reactive oxygen species (ROS) is stimulated by AGEs, this further intensifies the formation of AGE, forming a vicious cycle. AGEs are also antigenic and hence are able to elicit immune responses [10]. AGEs engage with certain cell-surface receptors (RAGE), which might result in either endocytosis and subsequent destruction or cellular activation and pro-oxidant or pro-inflammatory processes [12]. The generation of AGEs is primarily endogenous, although studies noted that AGEs is also generated from external sources, like food and tobacco use. Tissue levels of AGE rise with advancement in age [12].

AGEs have two (2) main types of cell surface receptors:

1. Scavenger receptors, which remove and degrade AGEs, and
2. Receptors for AGEs (RAGE),

RAGE is a type 1 transmembrane protein with 404 amino acid residues and an estimated 45 KDa N-terminal extracellular domain, and belongs to the superfamily of cell surface immunoglobulins, whose expression is increased in a number of disease conditions like atherosclerosis and Alzheimer's disease [13]. RAGE mediates interactions of AGEs. When it comes to controlling TNF-alpha production/expression, oxidative

stress, and endothelial dysfunction in type 2 diabetes, the AGE-RAGE signaling pathway plays a crucial role [14]. RAGE causes distinct cellular signaling reactions in response to AGE binding. RAGE binds numerous substances in addition to AGEs, including high mobility group protein B1, S100 calcium-binding proteins, calgranulin, amyloid- β-protein and amphotericin [34]. According to a study AGE-RAGE signals via transforming growth factor (TGF)-beta, nuclear factor-kB, mitogen-activated protein kinases (MAPK; ERK1/2, p38MAPK), and nicotinamide adenine dinucleotide oxidases (NOX) induce expression of vascular adhesion molecule 1, E-selectin, proinflammatory cytokines (IL-1β, IL-6, TNF- α) and vascular endothelial growth [14]. Vascular fibrosis, calcification, inflammation, prothrombotic effects, and subsequently vascular damage result from increased activation of the AGE-RAGE signaling pathways in vascular smooth muscle cells of DM subjects [35]. Atherosclerotic CVD in diabetic individuals and microvascular consequences such as diabetic nephropathy, retinopathy, and neuropathy are the overall effect of this is increased underlying processes. Growing evidence suggests that AGEs interaction with RAGE stimulates oxidative stress and has a significant role in the onset and progression of DM complications and CVDs [15]. Accompanying hypertension intensifies these complications and contributes to acceleration of vascular dysfunction. In human serum, a soluble form of RAGE designated (sRAGE) have recently been discovered. Although their precise function in circulation is uncertain, sRAGE may serve as an indicator of AGE-RAGE axis activity. In this regard, vascular complications have been shown to correlate with sRAGE plasma levels [16]. DM patients, have an increased concentrations of circulating AGEs and sRAGE in their tissue, which serves as a predictor of cardiovascular risk events and leading cause of death. According to some studies, soluble isoforms of RAGE serve dual purposes, one as preventive therapeutic target in diabetic patients as well as predicting cardiovascular outcomes in DM. As such, measurement of urinary and plasma AGE levels and sRAGE can serve as biomarkers for microvascular complications in DM [14].

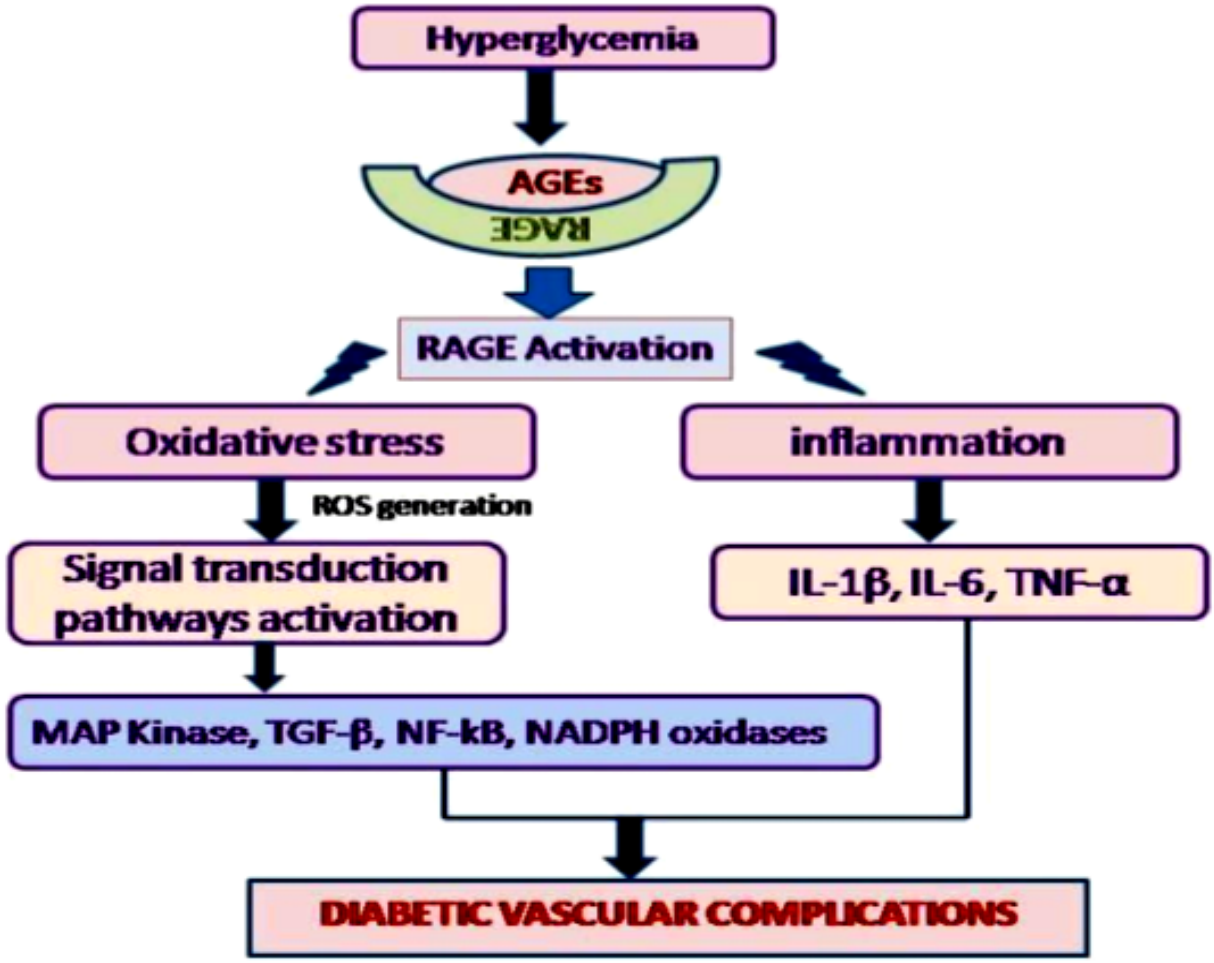

Figure 1: Role of AGEs and its receptor (RAGE)-mediated diabetic vascular complications. REGA; receptor of AGEs, AGEs; advanced glycation end products, TGF-β; transforming growth factor-beta, ROS; reactive oxidative species, IL-6; interleukin-6, IL-1β; interleukin-1beta, TNF-α; tumour necrotic factor-α, NADPH; nicotinamide adenine dinucleotide phosphate hydrogenase, NF-kB; Nuclear Factor Kappa-B-Cells B (Modified from Chawla and Tripathy 2019).

RAGE Gene Polymorphisms

Human RAGE gene was mapped in chromosome 6p21.3, located in the major histocompatibility complex locus in the class III regions. This gene comprises 1.7 kb, 11 exons and 10 introns of variable size in 3'UTR region, which may reach 4 kpb. Moreover, immunoglobulin type V domain is codified by the second and third exons [17]. Numerous alternatively spliced transcript variants encoding for the contrasting isoforms, and non-protein-coding variants, gene have been described, some of which might affect both the transcriptional activity and the binding affinity of RAGE to its ligands [9]. Genetic variations of RAGE are considered to be associated with the development of many disease conditions, especially those with persistent hyperglycemia and some neoplasm [18]. RAGE gene SNPs are incriminated in numerous pathological states, such as microvascular complications of DM, heightened inflammatory response, non-small cell lung cancer, gastric cancer, or breast cancer [17]. Barbezier et al. (2014) suggested that a combination of sRAGE and RAGE gene polymorphisms analysis might be an important clinical tool for predicting vascular diseases risk in DM subjects. Genetic investigations on the RAGE gene discovered around 30 polymorphisms at the exons, introns and in the 65 5'-flanking regions [10]. Most of these RAGE gene polymorphisms identified are associated with disease onset and/or increased susceptibility to diseases. However, some of these genetic polymorphisms might alter the RAGE gene activity after binding with AGE thereby influencing vascular complications development in diabetics [19]. As a result of an amino acid substitution of glycine for serine in domain V and two polymorphic areas in the promoter region, the RAGE gene has a lot of variants, including functional polymorphisms -429T/C (rs1800625); 1704G/ T (rs184003) in intron 7, -374T>A (rs 1800624), and G82S (rs2070600) in exon 3, have been implicated in the development of microvascular complications in DM [20]. Concise information would be elaborated on the five (5) main RAGE polymorphisms described in the literature which include rs2070600, rs1800624, rs1800625, rs184003, and a 63 bp deletion and whether or not they are associated with microvascular complications in DM [20]

RAGE Gene Polymorphisms and Microvascular Complications in DM: rs2070600 Polymorphism

The rs2070600, the most widely reported SNP of the RAGE gene as reported in the Human Gene Mutation Database (HGMD) [21]. This SNP is linked to microangiopathy in type 2 DM [17], and found in exon 3 of the RAGE gene. The SNP amplifies RAGEs stimulation by its ligands, prompting a proinflammatory signal which triggers inflammatory diseases underlying mechanisms [22]. Studies on type 2 DM, demonstrated a noteworthy connection between rs2070600 and retinopathy. Another remarkable association was report between rs2070600 and coronary artery diseases [23]. A study by Katrien et al. (2009) also reported strong relation between RAGE polymorphism Gly82Ser and circulating sRAGE levels with microvascular complications in a US population, indicating that subjects with CT genotype had lower levels of sRAGE and hence more susceptible to microvascular complications in DM. Katrien et al. (2009) further reported that the consequences of this polymorphism and the unique role of sRAGE levels in the development of vascular complications in DM need to be investigated further. According to researches the G82S mutation in RAGE exhibits improved ligand binding and downstream signaling that causes microvascular complications [24]. Asian populations have a significantly increased risk of developing diabetic retinopathy due to the Gly82Ser polymorphism. Although the precise mechanism by which RAGE signaling causes microvascular complications in T2DM patients has not yet been fully elucidated, it is hypothesized that retinal and renal damage, which are signs of microvascular complications, is caused by NF-kB-mediated increase in expression of the pro-inflammatory and pro-fibrotic cytokine TGF- β [14]. Contrastingly, however, in a large multi-ethnic Asian patients type 2 DM cohort, The RAGE gene's Gly82Ser and rs2071288 SNP variants have been reported to have positive effects on sRAGE levels, and were inversely related to diabetic kidney disease, indicating no causal link [25]. Genetic variants of RAGE gene have only been linked to circulating levels of sRAGE but not renal function among Asians with type 2 diabetics in a study by genome-wide association study [25]. In another meta-analysis on the association of the G82S polymorphism of RAGE gene to coronary heart disease in China, reported no associations [26]. Another study in US found no proof connecting genetic determinants of sRAGE and any of chronic kidney disease and coronary heart disease, yet the study is unable to rule out the feasibility of modest association given more limited power for these outcomes [27].

rs1800624 Polymorphism

This SNP of RAGE gene is generally known as -374T>A in literatures, and also reported in HGMD [21] as the SNP that is linked to reduction in heart disease risk [21]. This SNP of the RAGE gene is located in it`s promoter region. The SNP was suggested to have originated from Africa [21]. The rs1800624 SNP is also connected to a rise in RAGE and sRAGE expression and therefore decreased susceptibility to microvascular complications in DM [28]. The sRAGE serving as endogenous antagonist which neutralises proinflammatory ligands which in turn cannot be able to activate the inflammatory pathways. Despite its role in reducing the risk of heart disease, rs1800624 SNP was described to be associated with development of various types of cancer, notably, breast and lung cancer development [17]. Furthermore, results of studies carried out by Bansal et al. (2013) in North Indian type 2 DM patients, showed that AA genotype of the rs1800624 variant is known to confer cardio-vascular protection, and therefore, patients with this SNP are less susceptible to microvascular complications

in DM. Tripathi et al. (2014) also in a study on Indian population, demonstrated that the two promoter SNPs of RAGE gene, -374T/A and _429T/C showed a disparate connection with respect to complications of diabetes. While the -429T/C SNP showed a substantial connection to the development of macrovascular diabetic problems, the rs1800624 SNP was found to confer some amount of protection against the development of vascular complications in DM. There is evidence that the -374T/A polymorphism represses the expression of the RAGE gene. RAGE gene expression is inversely correlated with its ability to bind ligand and results in transmission of lesser signals for pro-coagulant or pro-thrombotic genes, hence providing protection for the vasculature [24]. To further support the claim that 374T SNP is linked to a reduction in risk of vascular diseases in DM, Wang et al. (2012) in a meta-analysis in Chinese population did not find an association between the 74T/A SNP of RAGE with coronary artery disease. In a similar study conducted on African–Brazilians type 2 DM patients, investigated and found out that the -374A allele of the RAGE gene is linked to a reduction in risk of ischemic heart disease [29], which is in contrast to the above claims, however another study reported that functional rs1800624 in subjects with type 1 diabetes, RAGE gene polymorphism is linked to urinary protein and cardiovascular disease [30]

rs1800625 Polymorphism

This SNP is generally called -429T>C in literatures, and was also reported in HGMD (http://www.hgmd.cf) as being linked to retinopathy in diabetic subjects [17]. This polymorphism of rs1800625 SNP is found ahead of the rs1800624 in the RAGE gene promoter. This SNP has been suggested to have it`s descent in Africa and later distributed among other world population through migration. The rs1800625 SNP was discovered to be allied to rises in RAGE expression that may affect the pathogenesis of inflammatory diseases. There were several studies involving rs1800625 SNP in DM patients, with inconsistent findings. Generally, the rs1800625 SNP was found to be remarkably raised in type 2 DM patients having retinopathy, in contrast to DM subjects without retinopathy. It was also reported to be associated with the risk of development and early onset of diabetic nephropathy [17]. Moreover, a study in India by Tripathi et al., 2014, who reported that -429T/C (rs1800625) SNP showed significant link with regard to macrovascular complications development in DM patients. Polymorphism of the rs1800625 SNP promoter raises transcription of the RAGE gene. The release of proinflammatory cytokines and adhesion proteins, favours thrombosis and ultimately capillary leakage and occlusion which leads to vascular dysfunction, caused by enhanced accessibility of RAGE to boosts AGE binding and inducement of downstream signaling [17]. Furthermore, this claim supported that -429T/C is associated with a heighten susceptibility to microvascular complications in DM. Hudson et al. (2001) in a survey in the United State on patients with type 2 DM, found that the C allele of the –429 SNP in RAGE gene was related to retinopathy. However, Wang et al., (2012) reported a contradicting finding in a meta-analysis conducted on Chinese population with a data which doesn`t support linking the 429T/C SNP of RAGE gene to heart disease. It was therefore suggested that the importance of SNP as a risk predictor of coronary heart disease is probably negligible, hence its screening utility in asymptomatic individuals may not be justified [26].

rs184003 Polymorphism

These rs184003 SNP is the most recounted of the five RAGE gene SNPs. It is commonly known as 1704G/T [17]. The rs184003 SNP was reported to be linked to heighten risk of coronary heart disease development in a Chinese study. A meta-analysis carried out on Asian subjects discovered a connection between the SNP (rs184003) to raising risk of DM and retinopathy development. Recent studies reported that, SNPs and haplotypes in RAGE and IL-6 receptor gene and rs184003 interactions were strikingly linked to diabetic ischemic heart disease [31]. Contrary to above claims, a similar study in a Malaysian population reported that RAGE gene polymorphisms in 1704G/T (rs184003), Gly82S and 2184A/G SNPs are not implicated in retinopathy development [32]. The study by Ng et al., (2011), however, claimed to be the first showing another less studied SNP, 2245A allele, of RAGE gene is linked to retinopathy development.

A 63bp Deletion (-421 to -359del) Polymorphism

The A 63bp Deletion or -421 to -359 deletion is a rare variant SNP and one of the most reported SNPs of RAGE gene. That was also reported by HGMD [21] and found to be linked to decreased survivability to heart disease in DM patients [17]. This SNP variant, which overlaps with rs1800624 and is posterior to rs1800625, is situated in the RAGE gene promoter. It results in the surge of transcriptional activity of RAGE. previous studies also reported that a 63bp deletion in RAGE gene is affiliated to a lowered incidence of diabetic nephropathy in type 2 DM [33].

Table I: Five (5) common RAGE gene SNPs with their Associated Vascular Complications in DM

RAGE Gene SNP	Associated DM Complication	Region/Race	Reference
rs2070600	Increased risk microangiopathy in type 2 DM	-	Serveaux-Dancer et al. (2019)
(Gly82Ser or G82S)	Increased risk diabetic retinopathy	China	González-Guerrero et al. (2024)
	Increased risk microvascular complications	United State	Alnaji et al., (2024)
	Increased risk diabetic retinopathy	Asia	Alnaji et al., (2024)
	No link with diabetic nephropathy	Asia	Lim et al. (2016)
	No link with coronary artery disease	China	Grauen et al. (2024)
	Unconclusive association with chronic kidney disease and coronary artery disease	United State	Maruthur et al. (2015)
rs1800624	Reduced Risk of vascular diseases	-	Serveaux-Dancer et al. (2019).
-374T>A	Decreased risk of microvascular complications in DM	-	Grauen et al., (2024)
	Confer cardiovascular protection in DM	North Indians	Tariq et al., (2024)
	Protective to microvascular complications	India	Tripathi et al. (2014)
	No significant association with coronary artery disease	Chinese	Grauen et al. (2024)
	Decreased risk of ischemic heart disease	African–Brazilians	González-Guerrero et al., (2024)
	Associated with proteinuria and cardiovascular disease in type 1 diabetic patients.	-	Rojas et al., (2024)
rs1800625	Associated with diabetic retinopathy	-	Serveaux-Dancer et al. (2019).
-429T>C	Associated with macrovascular complication in diabetic patients	India	Tripathi et al. (2014)
	Related to retinopathy in DM	United State	Arnesa et al., (2024)
	No significant association with coronary artery disease.	China	Grauen et al. (2024)
rs184003	Higher risk of diabetic retinopathy	Asia	Serveaux-Dancer et al. (2019)
1704G/T	Associated with diabetic ischemic heart disease	Asia	Liu et al. (2021)
	No association with diabetic retinopathy	Malaysia	Alnaji et al., (2024)
A 63bp Deletion	Reduced survival from heart disease in patients with DM	-	Serveaux-Dancer et al. (2019).
(-421 to -359del)	Associated with lower frequency of diabetic nephropathy	-	Arnesa et al., (2024)

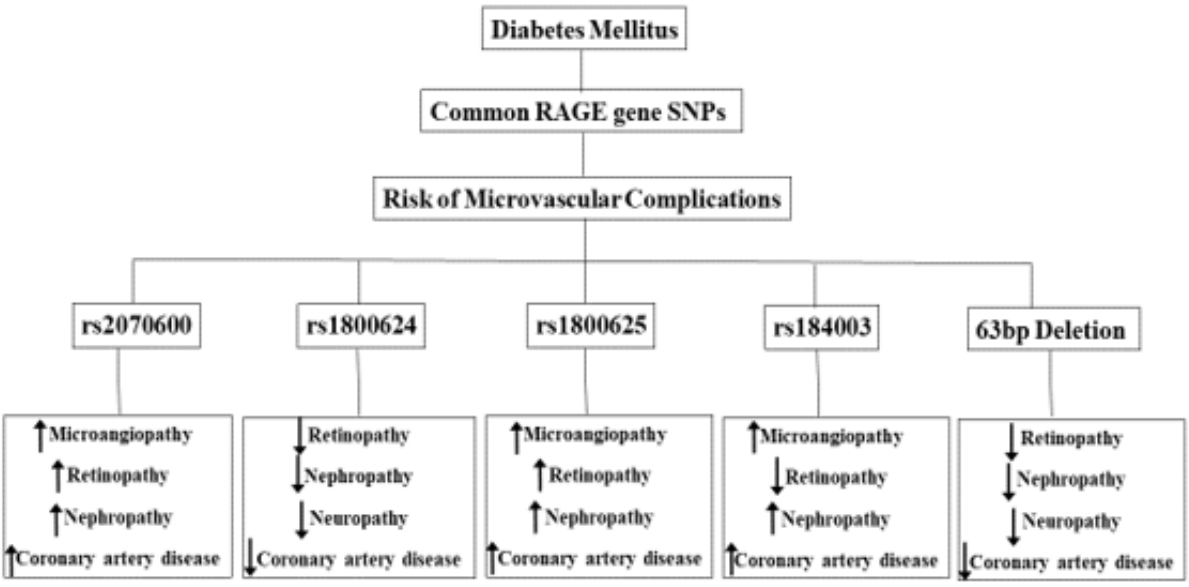

Figure 2: Connection of the five common SNPs of RAGE gene with Microvascular Complications in Diabetes Mellitus. ↑ =Increased risk of microvascular complications; ↓ = Decreased risk of microvascular complications.

CONCLUSION

AGE-RAGE signaling pathway plays a pivotal role in development and progression of microvascular complications in DM. RAGE mediates interactions of AGEs and therefore is a critical determinant in development of microvascular complications in DM. Many genetic variations of RAGE have been identified which are considered to be associated with increase or decrease in the risk of microvascular complications in DM with some conflicting findings. The rs2070600 (Gly82Ser or G82S) was reported to be linked to microangiopathy in type 2 DM. The -374T>A is being linked with a reduced risk of microvascular complications in DM. -429T>C is being related to diabetic retinopathy. The 1704G/T (rs184003) SNP was reported to be linked to an elevated risk of coronary heart disease development in Chinese study. A 63bp deletion in RAGE gene in type 2 DM subjects is linked to lower frequencies of diabetic nephropathy. So far, no research has been carried out on the roles played by RAGE gene in the development of microvascular complications in DM in African population.

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