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Determination of the role of RAGE rs1800625 polymorphism in diabetic retinopathy in South Asian Population

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ABSTRACT. Diabetic retinopathy, a complication of diabetes and a leading cause of visual impairment is a significant global public health concern. The study aimed to investigate the role of RAGE rs1800625 single nucleotide polymorphism in the development of diabetic retinopathy (DR) susceptibility in South Asian cohort of Pakistani decent. A panel of individuals consisting of diabetic retinopathy (DR), diabetic non-retinopathy (DNR) and healthy controls was screened for single nucleotide polymorphism (SNP), in promoter region of RAGE rs1800625 by polymerase chain reaction and restriction fragment length polymorphism method. Genotype-phenotype association was assessed by univariate logistic regression analysis. The RAGE SNP rs1800625 revealed a marginally significant association in DR when compared to the controls group under recessive model (RM: OR=0.09, [95%CI=0.0-1.30], p=0.05). The significant difference in genotype frequency resulting and marginal association of rs1800625 in RAGE points to it likely association with DR development. However, a study of larger sample size in other ethnicities is suggested to establish its exact role in DR development. rs1800625.

Key words: RAGE; Proliferative diabetic retinopathy; Advanced glycation end products; Genetic association.

INTRODUCTION

Diabetes, a type of metabolic disorder, is characterized by hyperglycemia and has an increasing global burden. Diabetic retinopathy is a type of diabetes induced microvascular complication. It is one of the leading causes of vision loss worldwide (Lee JY et al., 2025; Hou X et al., 2023; Flaxman SR et al., 2024). The Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) states that almost 28.8% diabetic patients undergo early DR onset, whereas 22.2% do not develop DR. The study proposes that there could be various genetic factors predisposing to certain individuals towards DR onset unlike others (Abhary S et al., 2009; Klein R et al., 1984). Such genetic factors can play a role in triggering DR related different processes.

An important factor involved in DR pathology is AGEs defined as non-enzymatically glycated proteins and lipids formed in hyperglycemia. Different functional studies have reported the importance of molecular interaction between advanced glycation end products (AGEs) and RAGE (Yamagishi S, 2011; Liu J et al., 2023). Under hyperglycemic conditions, there is an accumulation of AGEs in diabetic patients, consequently the interaction of AGEs with RAGE triggers up oxidative stress and inflammatory pathways, this interaction leads to vascular damage in the retina (Vazzana N et al., 2009; Gomułka K et al., 2023). The AGE-RAGE interaction has been known to be involved in triggering endothelial dysfunction and inflammation in DR development (Ulrich P et al., 2001; Lu Z et al., 2023; Zhou M et al., 2024; Taguchi K et al., 2023; Oshitari T, 2023).

The genetic polymorphisms in RAGE gene have reported to be associated with different ethnicities worldwide (Niu W et al., 2012; Balasubbu S et al., 2010; Radha V et al., 2002; Zong H et al., 2011), including Pakistani population where non-significant results were reported for its association with DR (Khan N et al., 2022) In addition, previous studies have also reported the role of certain polymorphisms in the RAGE including –374T/A and Gly82Ser to influence the susceptibility (Kang P et al., 2012), to diabetic retinopathy where the –374T/A variation was observed to have a protective effect, while the Gly82Ser polymorphism was found to increase the DR risk, particularly in Asian populations (Yuan D et al., 2012). In the current study rs1800625 (−429T>C)] SNP was selected to assess its role in DR cohort of south Asian population of Pakistani decent.

MATERIALS AND METHODS

In the current study, a case-control association analysis was performed on South Asian population of Pakistani decent having type 2 diabetic patients with DR. The study was conducted from April to October 2024 at Translational Genomics Lab COMSATS University Islamabad and the sample was collected from Mayo Hospital Lahore. The study panel was divided into three major groups, DR, diabetic non-retinopathy (DNR) and controls. The DR and DNR subjects were positive for T2DM with a fasting glucose level ≥106mg/dL and were diabetic for more than ten years. DR subjects were also having retinopathy confirmed by a retinal exam using fundoscopy and ophthalmoscopy. DR subjects were sampled based on their disease progression and were further divided into NPDR and PDR.

DNA extraction and genotyping

The blood samples were stored in ethylene diamine tetra acetic acid (EDTA) vacutainers and placed at 4oC. The DNA was extracted using phenol/chloroform protocol proposed by Sambrook J and Russell DW, 2006. The genotyping was done by PCR-RFLP. The primers used were the same as reported by Khan N et al., 2023.

Statistical analysis

The genotyping results obtained were analyzed by univariate logistic regression analysis or odds ratio. Results were considered statistically significant with a p value ≤0.05. To determine the involvement of selected SNP in disease development, different comparisons were conducted including DR comparison with control, DNR comparison with control and DR compared to DNR comparison among overall and gender wise groups. To find the role of the SNPs in disease progression, comparisons based on clinical stage of the disease were also performed that included PDR compared to NPDR, PDR compared to control, NPDR compared to control, PDR compared to DNR and NPDR compared to DNR.

Ethics approval of research

The study was approved by the Ethical review board of the Department of Biosciences, COMSAT University Islamabad. The study conformed to the Helsinki declaration and the sample collection was done after an informed written consent.

RESULTS

In the current study, a case-control association study was carried out to demostrate the genetic association of RAGE SNP rs1800625 in the development of DR in T2DM subjects of south asian population. The genetic analysis of RAGE SNP revealed a marginally significant association with DR when compared to controls (RM: OR=0.09, [95%CI=0.0-1.30], p=0.05; Table 1). Apart from these findings, other comparisons did not show any other significant association (Table 2,4 and 5) except for significant difference in genotype distribution in females (Table 3).

DISCUSSION

The analysis of rs1800625 polymorphism revealed a significant association with retinopathy in the overall population and female gender. The CC genotype was marginally more frequent in controls as compared to DR subjects in which it was completely absent. The CC genotype seemed to have a protective role against the development of DR in a recessive manner. This is evident by the higher proportion of heterozygotes in DR and diabetics as compared to controls which probably are associated with lower RAGE expression. Hence, it can be predicted that the CC genotype is probably associated with lower RAGE expression, however, functional analysis is needed to support this observation. While in case of female gender, the CC genotype was possessed by the control group only and it was completely absent in the DR and DNR. However, statistically significant association was only observed when comparing DNR with controls. This could mean that there is a marginal role of this SNP in the development of diabetes. Apart from the overall group and the female gender, no significant association was found with the progression of the disease. Although,

Table 1. RAGE rs1800625 chi square and logistic regression analysis of DR, DNR and control subjects' data.

Genotype	Controls (N= 200)	DR (N=160)	DNR (N=193)	DR vs. Controls			DNR vs. Controls			DR vs. DNR		
				χ^2 (p)	Z (p)	OR (95%CI) (p)	χ^2 (p)	Z (p)	OR (95%CI) (p)	χ^2 (p)	Z (p)	OR (95%CI) (p)
CC	6 (3%)	0 (0%)	2 (1.0%)		**2.21 (0.03)**	DM: 1.47 (0.86-2.52)		1.38 (0.17)	DM: 1.19 (0.70-2.03)		1.29 (0.20)	DM: 1.23 (0.72-2.10)
CT	30 (15%)	39 (24.4%)	38 (19.7%)	**9.33 (0.009)**	**2.25 (0.03)**	0.15 **RM: 0.09**	3.20 (0.20)	1.23 (0.22)	0.53 RM: 0.34	2.70 (0.26)	1.06 (0.29)	0.44 RM: 0.24
TT	164 (82%)	121 (75.6%)	153 (79.3%)		1.48 (0.12)	**(0.0-1.30) 0.05**		0.68 (0.49)	(0.05-1.88) 0.29		0.82 (0.41)	(0.0-4.63) 0.25
Allele frequency	**Controls** (N= 400)	**DR** (N=320)	**DNR** (N=386)	**DR vs. Controls**			**DNR vs. Controls**			**DR vs. DNR**		
				χ^2 (p)		OR (95%CI) (p)	χ^2 (p)		OR (95%CI) (p)	χ^2 (p)		OR (95%CI) (p)
C	42 (10.5%)	39 (12.2%)	42 (10.9%)	0.51 (0.48)		1.18 (0.73-1.93) 0.48	0.03 (0.86)		1.04 (0.65-1.68) 0.91	0.29 (0.59)		1.14 (0.70-1.85) 0.64
T	358 (89.5%)	281 (87.8%)	344 (89.1%)									

N: Number; DR: Diabetic retinopathy; DNR: Diabetic non-retinopathy; OR: Odds ratio; CI: Confidence interval; DM: Dominant model; RM: Recessive model
Ancestral allele/risk allele: C; Variant allele/non-risk allele: T. The bold values represent significant associations

Table 2. RAGE rs1800625 chi square and logistic regression analysis in male DR, DNR and control members.

Genotype	Controls (N=100)	DR (N=77)	DNR (N=94)	DR vs. Controls			DNR vs. Controls			DR vs. DNR		
				χ^2 (p)	Z (p)	OR (95%CI) (p)	χ^2 (p)	Z (p)	OR (95%CI) (p)	χ^2 (p)	Z (p)	OR (95%CI) (p)
CC	2 (2%)	0 (0%)	2 (2.1%)		1.25 (0.21)	DM: 1.71 (0.80-3.65)		0.06 (0.95)	DM: 1.08 (0.50-2.33)		1.29 (0.20)	DM: 1.58 (0.74-3.39)
CT	17 (17%)	22 (28.6%)	17 (18.1%)	4.70 (0.09)	1.84 (0.07)	0.15 RM: 0.25	0.05 (0.98)	0.20 (0.84)	0.86 RM: 1.07	4.07 (0.13)	1.63 (0.10)	0.21 RM: 0.24
TT	81 (81%)	55 (71.4%)	75 (79.8%)		1.50 (0.14)	(0.0-5.02) 0.26		0.21 (0.83)	(0.11-10.84) 1.00		1.27 (0.20)	(0.0-4.72) 0.25
Allele frequency	**Controls** (N=200)	**DR** (N=154)	**DNR** (N=188)	**DR vs. Controls**			**DNR vs. Controls**			**DR vs. DNR**		
				χ^2 (p)		OR (95%CI) (p)	χ^2 (p)		OR (95%CI) (p)	χ^2 (p)		OR (95%CI) (p)
C	21 (10.5%)	22 (14.3%)	21 (11.2%)	1.17 (0.28)		1.42 (0.72-0.82) 0.33	0.05 (0.83)		1.07 (0.54-2.13) 0.87	0.75 (0.39)		1.32 (0.67-2.63) 0.42
T	179 (89.5%)	132 (85.7%)	167 (88.8%)									

N: Number; DR: Diabetic retinopathy; DNR: Diabetic non-retinopathy; OR: Odds ratio; CI: Confidence interval; DM: Dominant model; RM: Recessive model
Ancestral allele/risk allele: C; Variant allele/non-risk allele: T. The bold values represent significant associations

Table 3. RAGE rs1800625 chi square and logistic regression analysis in female, DNR female and controls.

Genotype	Controls (N= 100)	DR (N=83)	DNR (N=99)	DR vs. Controls			DNR vs. Controls			DR vs. DNR		
				χ^2 (p)	Z (p)	OR (95%CI) (p)	χ^2 (p)	Z (p)	OR (95%CI) (p)	χ^2 (p)	Z (p)	OR (95%CI) (p)
CC	4 (4%)	0 (0%)	0 (0%)		1.84 (0.07)	DM: 1.26 (0.56-2.83)		**2.01 (0.04)**	DM: 1.31 (0.61-2.84)		0 (1)	DM: 0.96 (0.44-2.08)
CT	13 (13%)	17 (20.5%)	21 (21.2%)	4.94 (0.09)	1.36 (0.20)	0.57 RM: 0.13 (0.0-2.0) 0.06	**6.03 (0.05)**	1.54 (0.12)	0.48 RM: 0.11 (0.0-1.67) 0.06	0.02 (0.90)	0.12 (0.90)	1.00 RM: 1.19 (0-1263343) 0.46
TT	83 (83%)	66 (79.5%)	78 (78.8%)		0.60 (0.55)			0.76 (0.45)			0.12 (0.90)	
Allele frequency	**Controls** (N=200)	**DR** (N=166)	**DNR** (N=198)	**DR vs. Controls**			**DNR vs. Controls**			**DR vs. DNR**		
				χ^2 (p)		OR (95%CI) (p)	χ^2 (p)		OR (95%CI) (p)	χ^2 (p)		OR (95%CI) (p)
C	21 (10.5%)	17 (10.2%)	21 (10.6%)	0.007 (0.93)		0.97 (0.47-2.01) 1.00	0.001 (0.98)		1.01 (0.51-2.01) 1.00	0.01 (0.91)		0.96 (0.47-1.99) 1.00
T	179 (89.5%)	149 (89.8%)	177 (89.4%)									

N: Number; DR: Diabetic retinopathy; DNR: Diabetic non-retinopathy; OR: Odds ratio; CI: Confidence interval; DM: Dominant model; RM: Recessive model
Ancestral allele/risk allele: C; Variant allele/non-risk allele: T. The bold values represent significant associations

Table 4. RAGE rs1800625 chi square and logistic regression analysis of in PDR, NPDR and controls.

Genotype	Controls (N= 200)	NPDR (N=90)	PDR (N=70)	NPDR vs. Controls			PDR vs. Controls			PDR vs. NPDR		
				χ^2 (p)	Z (p)	OR (95%CI) (p)	χ^2 (p)	Z (p)	OR (95%CI) (p)	χ^2 (p)	Z (p)	OR (95%CI) (p)
CC	6 (3%)	0 (0%)	0 (0%)		1.66 (0.10)	DM: 1.56 (0.83-2.95)		1.47 (0.14)	DM: 1.35 (0.66-2.75)		0 (1)	DM: 0.86 (0.39-1.91)
CT	30 (15%)	23 (25.6%)	16 (22.9%)	**6.93 (0.03)**	**2.15 (0.03)**	0.16 RM: 0.17 (0.0-2.33) 0.21	4.13 (0.13)	1.50 (0.13)	0.38 RM: 0.21 (0.0-3.01) 0.20	0.16 (0.69)	0.39 (0.69)	0.72 RM: 1.28 (0.0-1363147) 0.44
TT	164 (82%)	67 (74.4%)	54 (77.1%)		1.48 (0.14)			0.89 (0.38)			0.39 (0.69)	
Allele frequency	**Controls** (N= 400)	**NPDR** (N=180)	**PDR** (N=140)	**NPDR vs. Controls**			**PDR vs. Controls**			**PDR vs. NPDR**		
				χ^2 (p)		OR (95%CI) (p)	χ^2 (p)		OR (95%CI) (p)	χ^2 (p)		OR (95%CI) (p)
C	42 (10.5%)	23 (12.8%)	16 (11.4%)	0.65 (0.42)		1.23 (0.70-2.22) 0.48	0.09 (0.76)		1.10 (0.57-2.10) 0.75	0.13 (0.71)		0.88 (0.42-1.83) 0.73
T	358 (89.5%)	157 (87.2%)	124 (88.6%)									

N: Number; DR: Diabetic retinopathy; DNR: Diabetic non-retinopathy; OR: Odds ratio; CI: Confidence interval; DM: Dominant model; RM: Recessive model
Ancestral allele/risk allele: C; Variant allele/non-risk allele: T. The bold values represent significant associations

Table 5. RAGE rs1800625 chi square and logistic regression analysis of the genotype and allele frequency of RAGE rs1800625 in NPDR, PDR and DNR individuals.

Genotype	DNR (N=193)	NPDR (N=90)	PDR (N=70)	NPDR vs. DNR			PDR vs. DNR		
				χ^2 (p)	Z (p)	OR (95%CI) (p)	χ^2 (p)	Z (p)	OR (95%CI) (p)
CC	2 (1.0%)	0 (0%)	0 (0%)	2.09 (0.35)	0.97 (0.33)	DM: 1.31 (0.70-2.46) 0.36	1.01 (0.60)	0.85 (0.39)	DM: 1.13 (0.56-2.29) 0.73
CT	38 (19.7%)	23 (25.6%)	16 (22.9%)		1.12 (0.26)	RM: 0.42 (0.0-8.27) 0.55		0.56 (0.57)	RM: 0.54 (0.0-10.67) 0.18
TT	153 (79.3%)	67 (74.4%)	54 (77.1%)		0.91 (0.36)			0.37 (0.71)	
Allele frequency	**DNR** (N=386)	**NPDR** (N=180)	**PDR** (N=140)	**NPDR vs. DNR**			**PDR vs. DNR**		
				χ^2 (p)		OR (95%CI) (p)	χ^2 (p)		OR (95%CI) (p)
C	42 (10.9%)	23 (12.8%)	16 (11.4%)	0.008 (0.93)		1.25 (0.70-2.22) 0.48	0.002 (0.96)		1.10 (0.57-2.10) 0.75
T	344 (89.1%)	157 (87.2%)	124 (88.6%)						

N: Number; DR: Diabetic retinopathy; DNR: Diabetic non-retinopathy; OR: Odds ratio; CI: Confidence interval; DM: Dominant model; RM: Recessive model
Ancestral allele/risk allele: C; Variant allele/non-risk allele: T. The bold values represent significant associations

a higher frequency of heterozygotes was observed in DR and its subtypes, which probably have some functional implication. The SNP of RAGE (rs1800625 also shows varying results in different populations probably due to its ethnicity specific role in the disease. Association of the C allele has been demonstrated with PDR in Caucasians (Hudson BI et al., 2001); however, no such association was found in Chinese DR patients (JiXiong et al. 2003; Khan N et al., 2022). The role of RAGE in DR can be understood by looking at the role of endogenous secretory RAGE (esRAGE), which is a variant formed due to alternative splicing. The esRAGE when administered to diabetic mice, reduces atherogenesis (Yonekura H et al., 2003). Studies have also shown reduced levels of esRAGE in individuals with diabetes and cardiovascular disease and these levels were found to be associated with cardiovascular disease and renal disease (Yonekura H et al., 2003). It has been suggested that factors involved in RAGE expression also affect esRAGE expression in vivo (Kalousová M et al., 2007). In a Chinese study on T2DM patients, the rs1800625 (-429T>C) has been reported to be associated with esRAGE expression (Peng WH et al., 2009). Hence, this can be proposed that polymorphisms that effect RAGE expression also alter esRAGE expression, hence change disease susceptibility. In the present study, it can be proposed CC genotypes of rs1800625 SNP can be involved in increasing the esRAGE expression, thus the availability of secretory RAGE is increased and the AGEs produced in diabetic conditions are bound up by them. Therefore, the pathogenic effects of AGEs are inhibited, and a protective effect is observed. However, functional analysis needs to be carried out to support this hypothesis.

CONCLUSIONS

In conclusion, the current study demonstrates that RAGE polymorphism had a minor role and was found to be somewhat disease associated in nature. Differences in the association of the

polymorphism exist with various diseases in different populations, these may be due to biasness in sample recruitment, samples sizes, diverse inclusion and exclusion criteria, variations in demographics of different regions and ethnicities. Such association studies enable the identification of possible genetic factors in various multifactorial diseases in different ethnic groups. Future research with larger sample size can help in establishing the exact role of RAGE rs1800625 in diabetic cases.

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CONFLICT OF INTEREST

The author declares no conflict of interest.

REFERENCES

Abhary S, Hewitt AW, Burdon KP, Craig JE. (2009). A systematic meta-analysis of genetic association studies for diabetic retinopathy. *Diabetes.* 58: 2137–47.

Balasubbu S, Sundaresan P, Rajendran A, Ramasamy K, et al. (2010). Association analysis of nine candidate gene polymorphisms in Indian patients with type 2 diabetic retinopathy. *BMC Med Genet.* 11: 158.

Flaxman SR, Bourne RRA, Resnikoff S, Ackland P, et al. (2024). Global causes of blindness and distance vision impairment 1990–2020: a systematic review and meta-analysis. *Lancet Glob Health.*12: e57–72.

Gomułka K, Ruta M. (2023). The Role of Inflammation and Therapeutic Concepts in Diabetic Retinopathy—A Short Review. *Int J Mol Sci.* 24: 1024.

Hou X, Wang L, Zhu D, Guo L, et al. (2023). Prevalence of diabetic retinopathy and vision-threatening diabetic retinopathy in adults with diabetes in China. *Nat Commun.* 14: 4296.

Hudson BI, Stickland MH, Futers TS, Grant PJ. (2001). Effects of novel polymorphisms in the RAGE gene on transcriptional regulation and their association with diabetic retinopathy. *Diabetes.* 50: 1505–11.

Kalousová M, Jáchymová M, Mestek O, Hodková M, et al. (2007). Receptor for advanced glycation end products—soluble form and gene polymorphisms in chronic haemodialysis patients. *Nephrol Dial Transplant.* 22: 2020–6.

Kang P, Tian C, Jia C. (2012). Association of RAGE gene polymorphisms with type 2 diabetes mellitus, diabetic retinopathy, and diabetic nephropathy. *Gene.* 500: 1–9.

Khan N, Paterson AD, Roshandel D, Maqbool S, et al. (2023). Role of 19 SNPs in 10 genes with type 2 diabetes in the Pakistani population. *Gene.* 848: 146899.

Klein R, Klein BE, Moss SE, Davis MD, et al. (1984). The Wisconsin Epidemiologic Study of Diabetic Retinopathy. II. Prevalence and risk of diabetic retinopathy when age at diagnosis is less than 30 years. *Arch Ophthalmol.* 102: 520–6.

Koyama H, Shoji T, Fukumoto S, Shinohara K, et al. (2007). Low circulating endogenous secretory receptor for AGEs predicts cardiovascular mortality in patients with end-stage renal disease. *Arterioscler Thromb Vasc Biol.* 27: 147–53.

Lee JY, Bae K, Lee S, Park SK. (2025). Nationwide trends and incidence of blindness in patients with diabetic retinopathy identified using an age-period-cohort analysis. *Eye (Lond).* 39: 118–24.

Liu J, Pan S, Wang X, Liu Z, et al. (2023). Role of advanced glycation end products in diabetic vascular injury: molecular mechanisms and therapeutic perspectives. *Eur J Med Res.* 28: 553.

Lu Z, Fan B, Li Y, Zhang Y. (2023). RAGE plays key role in diabetic retinopathy: a review. *Biomed Eng Online.* 22: 128.

Niu W, Qi Y, Wu Z, Liu Y, et al. (2012). A meta-analysis of receptor for advanced glycation end products gene: four well-evaluated polymorphisms with diabetes mellitus. *Mol Cell Endocrinol.* 358: 9–17.

Oshitari T. (2023). Advanced Glycation End-Products and Diabetic Neuropathy of the Retina. *Int J Mol Sci.* 24: 2927.

Peng WH, Lu L, Wang LJ, Yan XX, et al. (2009). RAGE gene polymorphisms are associated with circulating levels of endogenous secretory RAGE but not with coronary artery disease in Chinese patients with type 2 diabetes mellitus. *Arch Med Res.* 40: 393–8.

Radha V, Rema M, Mohan V. (2002). Genes and diabetic retinopathy. *Indian J Ophthalmol.* 50: 5–11.

Sambrook J, Russell DW. (2006). Purification of nucleic acids by extraction with phenol:chloroform. *CSH Protoc.* 2006: pdb.prot4455.

Taguchi K, Fukami K. (2023). RAGE signaling regulates the progression of diabetic complications. *Front Pharmacol.* 14: 1128872.

Ulrich P, Cerami A. (2001). Protein glycation, diabetes, and aging. *Recent Prog Horm Res.* 56: 1–21.

Vazzana N, Santilli F, Cuccurullo C, Davì G. (2009). Soluble forms of RAGE in internal medicine. *Intern Emerg Med.* 4: 389–401.

Yamagishi S. (2011). Role of advanced glycation end products (AGEs) and receptor for AGEs (RAGE) in vascular damage in diabetes. *Exp Gerontol.* 46: 217–24.

Yonekura H, Yamamoto Y, Sakurai S, Petrova RG, et al. (2003). Novel splice variants of the receptor for advanced glycation end-products expressed in human vascular endothelial cells and pericytes, and their putative roles in diabetes-induced vascular injury. *Biochem J.* 370: 1097–1109.

Yuan D, Yuan D, Liu Q. (2012). Association of the receptor for advanced glycation end products gene polymorphisms with diabetic retinopathy in type 2 diabetes: a meta-analysis. *Ophthalmologica.* 227: 223–32.

Zhou M, Zhang Y, Shi L, Li L, et al. (2024). Activation and modulation of the AGEs-RAGE axis: Implications for inflammatory pathologies and therapeutic interventions—a review. *Pharmacol Res.* 206: 107282.

Zong H, Ward M, Stitt AW. (2011). AGEs, RAGE, and diabetic retinopathy. *Curr Diab Rep.* 11: 244–52.