28 Diabetic Retinopathy: Clinical, Genetic, and Health Economics (An Asian Perspective)

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Abstract

Diabetes mellitus is the fastest growing disease in the world that is estimated to reach nearly half a billion in 2045, and a third of them would have microvascular complication like diabetic retinopathy (DR). Hyperglycemia, hypertension, and dyslipidemia are some of the controllable risk factors. DR is classified into nonproliferative, proliferative, and macular edema types. Many molecular factors like *VEGF*, *ALR2*, *eNOS*, *MTHFR*, *ACE*, *IGF*, and *RAGE* and its associated single nucleotide polymorphisms play a critical role in the process of neovascularization. Some of the drug discovery and newer treatment regimens are based on these molecular factors. More research by the clinicians, epidemiologists, and vision scientists is necessary to reduce the visual morbidity and disease burden of DR in the community.

Keywords

Diabetic retinopathy · Health economics · Genetic susceptibility · Type 2 diabetes mellitus · Prevalence

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28.1 Introduction

28.1.1 Prevalence of Diabetes Mellitus (DM) and Diabetic Retinopathy (DR)

Diabetes mellitus (DM), a noncommunicable complexly origin disease, is considered as one of the most challenging health problems rising at a tremendous pace globally. DM is estimated to rise to 629 million by 2045 from 425 million in 2017 [1]. According to IDF 2017 report, 159 million in Western Pacific and 82 million in Southeast Asian adults are living with DM [1]. China, India, Indonesia, and Pakistan represent 48% of the global burden [1]. With the incidence of DM increasing at an alarming rate, the number of people with diabetic retinopathy (DR), a microvascular complication, is expected to surge from 126.6 million in 2010 to 191.0 million by 2030 [2]. DR ranks the fifth most common cause of global blindness (moderate and severe vision impairment) [3] accounting for 4.8% of the cases of blindness throughout the world [4]. It is one of the leading causes of visual impairment and blindness in the working-age population (24–70 years) in both developing and developed countries [5].

A pooled analysis of 22,896 people with DM from 35 population-based studies in the USA, Australia, Europe, and Asia (between 1980 and 2008) showed that the overall prevalence of

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any DR in T1DM (type 1 diabetes mellitus) and T2DM (type 2 diabetes mellitus)) was 34.6% (95%CI 34.5–34.8), with 10.2% having vision-threatening diabetic retinopathy (VTDR) [6].

The prevalence of DR appears to be higher in patients with T1DM than in those with T2DM [3]. Nearly all persons suffering from T1DM develop retinopathy, while more than 77% of persons with T2DM may develop retinopathy after 20 years' duration of diabetes [5], and approximately 25% of persons with DR may develop macular edema [7]. In India, the overall crude prevalence of DM is 4.7% in urban and 1.9% in rural areas [8], and 7.3–26.2% of these develop DR [9]. In a population-based door-to-door survey in the urban slums of Western India, we reported the DR prevalence of 1.41% in general population and 15.4% in type 2 DM [10]. The prevalence of severe retinopathy in patients with T1DM has diminished over the past 35 years due to improved medical care [11], but the recent epidemic of T2DM requires a new understanding of the biology of DM. The growing number of diabetic patients and the longer life span in aging population imply an increase in patients suffering from DR, which not only affects the quality of life of the individuals and their families but also increases the medical and economic burden of the society.

28.1.2 Social Burden and Health Economics

DM and its complications like DR impose a huge economic burden on the global healthcare. According to the International Diabetes Federation (IDF) estimation, globally USD 727 billion is spent for DM (20–79 years age group), whereas USD 850 billion was spent (19–99 years age group) in 2017. The expenditure on diabetes is projected to reach USD 776 billion (20–79 years age group) and USD 958 billion (18–99 years age group) by 2045 [1]. A recently published study from India estimated that the total annual expenditure on DM care was, on an average, INR (Indian rupee) 10,000 (USD 154) in urban areas and INR 6260 (USD 96.42) in rural areas [12]. Patients with DM having retinal complication spent approximately INR 13922 (USD 214.38) per month [12]. For a chronic disease like DM and hence DR, there is an unmet urgency for development of a cost-effective therapy that is dependent on a basic understanding of the pathophysiological progression of DR.

28.2 Patho-mechanisms and Biology of Retinopathy

Retinopathy is a slow-progressing disease, mainly characterized by damage of the microvasculature of the retina. The onset and progression of retinopathy are triggered by numerous factors including extended duration of diabetes, poor control of blood glucose, elevated blood pressure, and dyslipidemia [13–16].

Histological studies, using postmortem retinas of diabetic patients, have revealed several cellular changes: selective endothelial and mural cell loss (including pericytes), presence of mural cell ghosts, endothelial clusters, acellularity and microaneurysms [17, 18], basement membrane thickening, presence of hemorrhage in the inner nuclear layer (INL) and outer plexiform layer (OPL), as well as eosinophilic exudates in the OPL [18] .

Further, immunological and immunohistochemical studies have shown hypertrophy of Müller cells throughout the inner and outer diabetic retina and increased apoptosis [19]; expression of pro- and antiapoptotic molecules in ganglion and glial cells, respectively [20]; and elevated levels of vascular endothelial growth factor (VEGF) in retinal blood vessels of diabetic patients with pre-proliferative or no retinopathy stages [21]. Alternation in several other factors, including somatostatin [22], cortistatin [23], αA- and αB-crystallins, advanced glycation end products (AGEs), and receptor for AGE (RAGE) [24], as well as apolipoprotein A1 (ApoA1) [25], was also observed in the postmortem tissues.

Advanced molecular studies revealed abnormal levels of expression of mRNA and proteins of various chemokines [26, 27], cytokines [26–29], inflammatory markers [29–31], and

angiogenic factors [27, 29, 30, 32] in aqueous humor, serum, or urine from diabetic patients. Although these morphological and molecular studies provide a better picture of the pathogenesis of DR at a cell and molecular level, they failed to provide mechanistic biological pathway. However, based on these observations, several mechanisms and interlinked biological pathways such as hyperglycemia and oxidative stress-mediated AGE products and inflammation, endoplasmic stress (ES)-mediated unfolded protein response (UPR) and apoptosis, hypoxia- and ischemia-mediated angiogenesis, activation of protein kinase C, polyol production, and hexosamine pathways have been postulated to be responsible for retinopathy complications in DM [33–36]. As these mechanisms and pathways are interlinked [37], the strategies to prevent the development/progression of this complication become complicated.

28.3 Clinical Diagnosis and Classification of DR

From a clinical standpoint, it is clear that the primary driving factors in DR pathogenesis are uncontrolled hyperglycemia, hypertension, and dyslipidemia. However, recent evidences have also suggested neurodegeneration as an early event in the pathogenesis of DR [38].

The diagnosis of DR essentially remains clinical in nature, the gold standard being dilated eye exam and serial fundus images. DR is classified as either nonproliferative diabetic retinopathy (NPDR) or proliferative diabetic retinopathy (PDR) based on the presence of neovascularization that typifies the proliferative form [13]. Nonproliferative features of retinopathy, include microaneurysms, intraretinal hemorrhage, hard exudates, venous beading, and intraretinal microvascular anomalies (IRMAs), and the proliferative form features the neovascularization (NV) that bleeds easily resulting in vitreous hemorrhage, subsequent fibrosis, and tractional retinal detachment [39, 40]. DME characterized by increased vascular permeability and deposition of hard exudate at the central retina secondary to lipoproteins leaking from retinal capillaries into the extracellular space of the retina [41] is also a major cause of vision loss and can occur at any stage of DR.

IDF estimates globally 64% of people are living with DME, while 58% with DR face difficulties in performing daily activities [1]. Vision loss results from retinal detachment if patients are left untreated. Several emerging automated technologies have demonstrated promise in assisting with the diagnosis of sight-threatening DR leading to prompt referral for the timely management of the treatable conditions.

28.4 Genetics and Epigenetics of DR

DR is a complex disease, strongly influenced by both genetics and environment. Single nucleotide polymorphisms in genes encoding for the molecules and other enzymes, cytokines, and growth factors involved in DR pathophysiology have been associated with risk for DR in various populations. Among the candidate genes studied for variations and association with DR, *VEGF*, aldose reductase (*ALR2*), endothelial nitric oxide synthase (*eNOS*), methylene tetrahydrofolate reductase (*MTHFR*), and *RAGE* have been widely studied in various populations (Table 28.1).

Elevated serum and vitreous VEGF levels have been associated with PDR suggesting possible increase in *VEGF* gene expression in DR. The C(−634)G promoter *VEGF* polymorphism has been associated with risk for DR [67] and DME in Japanese cohorts [68], similarly G(−1154)A and C(− 7)T, and T(−1498)C polymorphisms are reported to be associated with risk for DR in Caucasian [69] and South Indian populations [70], respectively. *VEGF*-460C variation might accelerate the pathogenesis of retinal neovascularization in T2DM patients as suggested by association studies in Indian population [59]. In Chinese patients with T2DM, SNPs rs699947, rs833061, and rs13207351 at the promoter region of the *VEGF* gene might have association with predisposition DR [71].

Table 28.1 Genetic association studies for DR, PDR, and DME in various population

Gene	Chromosome location	Variation	Disease	Type	Association	Population	References
AR	7q35	C [-106] T, CC genotype	DR	T2DM	Significant association—risk	Iranian, Japanese, Egyptian	[42, 43]
			DR	T2DM	No significant association	Chinese	[44]
		C [-106] T, C allele	DR	T1DM	Significant association—risk	Asia, South America, Europe, and Australia	[45]
AKR1B1		-106C>T, [rs759853], TT genotype	DR	T2DM	Significant association—risk	North Indian population	[46]
		Z-2 Microsatellite	DR	T2DM	High risk	Asian Indian	[47]
			DR	T1DM/T2DM	Confer risk	White Ancestry	[48]
			DR	T2DM	Involved in the development of DR	Japanese population	[49]
			DR	T2DM	early onset of DR	Chinese population in Hong Kong	[50]
			DR	T2DM	Risk	Caucasian	[51]
		C[-12]G	DR	T2DM	Risk	China	[52]
		Z-4	DR	T1DM	Risk	Japanese	[53]
		Z+2	DR	T1DM	Confer protection against DR	White Ancestry	[48]
ALAR2		Z+2	DR	T2DM	associated with susceptibility to DR	South Indian Cohort	[54]
eNOS	7q36	VNTR 4b/a, a allele	PDR	T2DM	Significant association—risk	Slovenian	[45]
		T-786C & C774T	DR	T1DM	Risk for early onset severe DR	French	[55]
		Intron4 VNTR	DR	T2DM	Risk	Chinese, German, Japanese	[56]
			DME	T2DM	Risk	Japanese	[56]
RAGE	6p21.3	Gly82Ser, Ser82genotype	DR	T2DM	Significant association—risk	North Indian, Chinese	[45]
		-374A T/A	Sight threatening DR	T1DM	Risk associated	Scandinavian origin	[57]
		1704T allele	DR	DM	Risk associated	East Asian	[58]

VEGF	6p21	[-460 C/T], C allele	PDR, DR	T2DM	Significant association—risk	Indian, Caucasian	[45, 59]
		[+936C/T]	DR	T2DM	Positive association—risk	Asian	[45]
		[-2578C/A]	DR	T2DM	Significant association—risk	Chinese	[45]
		rs13207351	DR	T2DM	Positive association—risk	Chinese	[45]
		rs699947[-2578 A/C]	DR	T2DM	Positive association—risk	Asians and Europeans	[45]
		rs699947[-2578C/A]	DR	T2DM	Positive association—risk	Asians and Caucasians	[45]
		rs3025039[+936 C/T]	PDR	T2DM	Positive association—risk	Bengali Hindu	[45]
		rs2010963 [+405 G/C]	PDR	T2DM	Positive association—risk	Bengali Hindu	[45]
		rs2010963[-634G/C], C allele	DR	T2DM	Positive association—risk	Caucasian, Japanese	[45]
		rs2010963[-634G/C], C allele	DME	T2DM	Risk	Japanese	[45]
		+405CC genotype	DR	T2DM	Risk associated	Japanese	[60]
		CG genotype	DR	T2DM	Risk associated	Indian	[60]
		[-1154]C	DR	T2DM	Risk	Caucasian	[56]
		C[-634]G	DR	T2DM	Increase the risk for DR in patients with microalbuminuria	South Indian Cohort	[61]
ACE	17q23	Deletion polymorphism	Advanced DR	T2DM	Risk	Japanese	[56]
		Insertion/ Deletion	DR/NPDR	T2DM	Risk	Pakistani	[62]
PPARγ	3p25	Gly482Ser	DR	T2DM	Risk	Slovenia	[56]
Vit D receptor	12q13	Fok1 polymorphism	DR	T1DM	Risk	French	[56]
		Taq 1 Polymorphism	DR	T1DM	Tt- Risk in poor glycemic	French	[56]
Adiponectin	3q27	G276T	DR	T2DM	Risk	Japanese	[56]
MTHFR	1q36	C677T	DR	T2DM	Risk	Chinese	[56]
Glycoprotein	5q23	807T	Advanced stages of DR	T2DM	Risk	Sweden	[56]
TGFβ	9q13	R25P	PDR	T2DM	Risk	Caucasian	[56]
Neuro-peptide Y	7p15	L7P	DR	T2DM	Risk	Finnish	[56]
Alpha2/beta1 integrin	17q21	Intron 7 polymorphism	DR	T2DM	Risk	Japanese	[56]
HLA	6p21	DR9 & DQA1	DR	T1DM	Risk	Senegal	[56]

(continued)

Table 28.1 (continued)

Gene	Chromosome location	Variation	Disease	Type	Association	Population	References
MCP-I	17q11.2	rs1024611 [-2518 A/G] AA genotype	PDR	T2DM	Positive association—risk	Korean	[45]
		rs1024611 [-2518 A/G] G allele	PDR & NPDR	T2DM	Positive association—risk	Han Chinese	[45]
		rs1024611 [-2518 A/G] G allele	DR	T2DM	Increased onset	Japanese	[45]
MnSOD	6q25.3	A16V[C47T] AV genotype	DR	DM	Positive association—risk	North Iranian	[45]
iNOS	17q11.2	13-repeat genotype	DR	T2DM	associated with susceptibility to DR	South Indian Cohort	[54]
TNF	6p21.3	15-repeat genotype [β gene]	DR	T2DM	associated with susceptibility to DR	South Indian Cohort	[54]
		NcoI	PDR	T2DM	β2 allele is genetic factor for incidence of PDR	Caucasian – Slovak	[63]
		[GT]n microsatellite	DR, PDR	T2DM	Allele 4 [103 bp] is a low risk for developing retinopathy, Allele 8 [111 bp] is associated with PDR	Asian Indian	[64]
PEDF gene polymorphism	17p13.1	T130T	DR	T2DM	Moderate protective association	South Indian Cohort	[65]
IGF-1	12q23.2	promoter [CA] 18 repeat genotype	DR	T2DM for more than 15 years	high risk for developing DR and PDR	Southern Indian sample cohort	[66]

Among Chinese Han individuals with T2DM, polymorphism -634G/C of the *VEGF* gene was not correlated with NPDR or PDR; however, polymorphism-460C/T of the *VEGF* gene was correlated with NPDR, and C allele was associated with lower NPDR risk than T allele [72].

The gene *ALR2* that codes for aldose reductase, the rate-limiting enzyme of the polyol pathway, has a particular Z-2 promoter microsatellite repeat which has not only been associated with genetic susceptibility to DR in Caucasian [48, 73] and Asian Indian populations [47] with T2DM but also has been shown through functional studies to enhance gene expression in response to hyperglycemia. Also an association was observed between DR and the C-106 T, CC genotype in the T2DM patients in Iranian [42] and Japanese population [74] but not in Chinese population [44]. Kaur et al. reported significant association of *AKR1B1* -106C > T polymorphism (homozygous recessive TT genotype) with retinopathy in North Indian patients [75]. Studies from Asia, South America, Europe, and Australia showed an association between C(−106)T polymorphism and the risk of DR in T1DM but not type 2 DM [45]. The Z-4 allele was significantly associated with patients with proliferative retinopathy in Japanese population. While the same study reported an association of Z + 2 allele with patients without retinopathy [53], a South Indian study reported an association of Z + 2 allele with risk for DR [54]. Results on Z + 2 allele from T1DM white ancestors were comparable to Japanese study [48].

Increased production of nitric oxide by down-regulation of *eNOS* has been shown to result in angiogenesis in animal models [76]. The intron4 27-bp (*VNTR)* has been consistently associated with risk for DR in Japanese [77], German, and Caucasian [78] populations.

Ser82 allele in the *RAGE* gene is a low-risk allele for developing DR in Asian Indian patients with T2DM [54, 79], whereas Vanita V. showed significant association of p.Gly82Ser polymorphism in *RAGE* with DR in T2DM patients [80]. However, studies from Malaysia, the USA, Europe, and Asia reported no associations between *RAGE* polymorphisms and DR [45]. Lindholam (2006) reported an association between *RAGE*(−374 T/A) polymorphism and type 1 diabetes [57].

Saleem et al. (2015) observed a significant association between insertion deletion polymorphism rs4646994 in intron 16 and DR and NPDR, but not with PDR in Pakistani cohort [62]. Matsumoto reported significant association in Japanese population between the presence of the D allele polymorphism in the *ACE* gene and advanced diabetic retinopathy (ADR) in Japanese subjects with T2DM [81].

An 18-repeat polymorphism in the promoter of IGF-1 gene is a susceptibility genotype for DR, and its clinical severity in a Southern Indian cohort is found by Uthra et al. [66] who also reported lack of association of PRKCB1 gene promoter polymorphisms and moderate protective association of PEDF gene polymorphism with DR in the same cohort [65].

Monocyte chemoattractant protein-1 (*MCP-1*) is a chemokine specific for monocytes and basophils. *MCP-1* rs1024611 (−2518 A/G) AA genotype was significantly associated with PDR in T2DM in Korean patients. On the other hand, the G allele of the same polymorphism in Han Chinese patients was significantly associated with high-risk PDR in T2DM. A study in Japanese patients with T2DM also reported that the G allele was significantly associated with DR [45].

Single gene association studies have not been comprehensively informative about the role of the DNA polymorphisms in disease pathogenesis, and hence approaches like haplotype analysis, linkage disequilibrium, and functional studies are expected to throw more light in this area.

Analysis of a handful of genetic variations is often insufficient to understand the genetic etiopathology of polygenic disease as DR. Hence, researchers now rely on robust technologies such as genome-wide association studies. Imperatore et al. (1998), in their study on Pima Indians with T2DM, showed some evidence of linkage to chromosomes 3 (LOD = 1.36) and 9 (LOD = 1.46) for diabetic retinopathy, although the evidence was insufficient for genome-aide studies [82]. Looker et al. (2007) performed a genome-linkage

analysis for DR and found evidence of linkage to chromosome 1p (LOD = 3.1 by single-point analysis and 2.58 by multipoint analysis) [83]. Similarly, another study on Mexican Americans with T2DM revealed suggestive linkage on chromosome 3 (LOD = 3.41) and chromosome 12 (LOD = 2.47) [84]. However, fine mapping of critical genomic regions, which harbor possible susceptibility genes, has not yet been reported. Genome-wide meta-analysis performed by Grassi et al. (2011) identified an intragenic SNP on chromosome 6 rs227455, located more than 200 kb from two undesignated genes *LOC728275* and *LOC728316*, and rs10521145 in strong linkage disequilibrium with copy number variation CNVR6685.1 on chromosome 16 to have strong association with risk for sight-threatening DR [85]. A genome-wide association study on Taiwanese population reported a risk association of SNPs located in five novel chromosomal regions in and around *MYSM1*, *PLXDC2*, *HS6ST3*, and *ARHGAP22* genes; the latter two found to have significant role in endothelial cell angiogenesis and increased capillary permeability [86]. A three-stage genome-wide association study carried out in a Japanese cohort revealed a borderline significance of association of an intronic SNP in long intragenic noncoding RNA RP1-90 L14 adjacent to *KIAA1009/QN1/CEP162* gene, suggesting a possible role of ciliary-associated genes in the pathogenesis of DR due to the involvement of *CEP162* gene [87].

However, identification of genes and genetic variations conferring risk for the development of DR and recognition of pre-symptomatic individuals would have tremendous impact in the treatment of the disease-related complications and could be useful in genetic counselling.

28.5 Recent Advances in Genetics/Epigenetics in Understanding and Management of DR

With the current use of inhibitors for growth factors involved in the DR pathology such as bevacizumab, ranibizumab, and aflibercept (VEGF-Trap) [88], significant genotype-specific personalized management strategies for patients could evolve. Gene therapy experiments targeting renin angiotensin system (RAS) pathway and antioxidant enzyme activities are also underway owing to the limitations of the current inhibitor-based treatments, which collectively hold promise in the effective management of diabetic microvascular complications in the retina [89].

28.6 Future Trends

Research in DR has to be a concerted effort between the ophthalmologist, the epidemiologist, and the vision scientist. Such efforts have led to the current knowledge that we have in the field.

However, further research is needed to identify molecular genetics and biological factors that could be applied as early genetic or biomarkers to identify the target population to reduce the burden of visual impairment or blindness in a community. Besides, such pathway analysis would also lead to the discovery of newer drugs that would reduce the morbidity or disease burden. Granting agencies should focus on these areas of research as DM is one of the rapidly rising diseases with epidemic proportions.

Conflict of Interest None of the authors have any proprietary interests or conflicts of interest related to this submission.

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