ARVO EDUCATION COURSE

Saturday, April 22, 2023
1-5pm
New Orleans Ernest N. Morial Convention Center
New Orleans, La

Diabetic retinopathy: Moving the field forward

Course organizers

Renu A Kowluru, PhD, FARVO, Wayne State University, Kresge Eye Institute
Arup Das, MD, PhD, University of New Mexico School of Medicine, NM VA Health Care System

Presentations

Presenters and presentations may change.

Time	Topic	Speaker
8:00-8:05am	Welcome and introduction	**Organizer and Speaker:** **Renu Kowluru, PhD** Wayne State University, Detroit, MI Kowluru R anddiabetic retinopathy - PubMed (nih.gov)
8:05-8:30am	Clinical Overview of Diabetic Retinopathy	**Arup Das, MD, PhD, University of New Mexico, Albuquerque, NM** **Das A and clinical diabetic retinopathy - Search Results - PubMed (nih.gov)**
Understanding the complex interaction in the pathogenesis of diabetic retinopathy (DR) remains a big challenge as DR appears to be a disease with heterogenous phenotypes with multifactorial influence. In this review, we will examine the natural history and risk factors related to DR, emphasizing distinct clinical phenotypes, histological hallmarks, related molecular mechanisms and their natural course in retinopathy. We will also summarize the current treatment modalities and future directions. Thus, this lecture will give an overview of this diease that will be followed by indepth studies on different aspects of the pathogenesis, imaging and therapies.		
8:30-8:55am	Epidemiology and Systemic Risk Factors	**Tien Y. Wong, MD, PhD**, Tsinghua Medicine, Tsinghua University, Beijing, China Professor & Senior Advisor, Singapore National Eye Centre, Singapore Prof Wong Tien Yin | SCRI - Singapore Clinical Research Institute

Time	Topic	Speaker
1. Global trends in epidemiology of diabetic retinopathy 2. Update on major risk factors 3. New concepts and directions in research in epidemiology and risk factors of diabetic retinopathy		
8:55- 9:20am	Our Evolving Understanding of the Genetic Architecture of Diabetic Retinopathy	**Lucia Sobrin, MD, MPH** Mass Eye & Ear, Boston, MA Sobrin L and genetics and diabetic retinopathy - Search Results - PubMed (nih.gov)
The underlying genetic risk factors for developing diabetic retinopathy and its complications are not well understood but there is active research in this area. This presentation will review recent findings in the field, including results from genome-wide association studies and polygenic risk score studies. Ongoing investigations in the human genetics of diabetic retinopathy including pharmacogenetic studies will also be discussed.		
9:20-9:45am	Experimental Models and Endpoints in the Study of Diabetic Retinopathy'	**David A. Antonetti, PhD,** Kellogg Eye Center, University of Michigan, Ann Arbor, MI Antonetti D and experimental models and diabetic retinopathy - Search Results - PubMed (nih.gov)
Recent research has rapidly improved our understanding of diabetic retinopathy and has led to updated characterization of the disease process including both vascular and neuronal changes. Vascular changes in permeability and fluid accumulation lead to diabetic macular edema while changes in vascular growth lead to neovascularization. However, other patients demonstrate retinal neurodegeneration without overt vascular changes. Current therapies targeting vascular endothelial growth factor have profoundly impacted care for this disease. Recent focus of research has explored the relationship of the retinal vessels and the retinal neural tissue with a developing appreciation for the requirement for this proper interaction of neurons, glia, microglia, pericytes and vascular endothelium for the proper functioning of the retina. This elegant interaction has been referred to as the neurovascular unit and contributes to the proper function of the retina including formation of the blood-retinal barrier allowing control of the neural environment. In diabetes this normal framework of interaction is profoundly dysregulated as part of the disease process. In this talk, I will discuss the genetic studies establishing the signaling pathways that drives development of the blood vessels (angiogenesis) and the blood-retinal barrier (barriergenesis) that emanate from the neural tissue. I will then discuss the alterations to the retinal vasculature in diabetes associated with changes in signaling factors controlling angiogenesis and barriergenesis as well as inflammation providing potential novel points of intervention. Finally, a potential model for diabetic retinopathy disease process that incorporates the neural-vascular interaction will be presented.		
9:45-9:55am	Discussion	
9:55-10:10am	Morning break	

Time	Topic	Speaker
10:10-10:35am	Molecular Mechanisms of Diabetic Retinopathy	**Julia Busik, PhD** Michigan State University, Lansing, MI Busik J and diabetic retinopathy - Search Results - PubMed (nih.gov)
Diabetic Retinopathy (DR), the most common microvascular complication of diabetes, is one of the leading causes of vision impairment in the world. Pathophysiology of this complex and multifactorial disease has been studied for many decades with multiple molecular mechanisms identified in the development and progression from early nonproliferative to advanced proliferative stages of the disease. Among these are several hyperglycemia-induced pathways, including aldose reductase activation and polyol pathway, hexosamine pathway, advanced glycation end-product (AGE) formation, activation of protein kinase C, activation of thioredoxin interacting protein (TXNIP). Dyslipidemia-induced pathways include dysregulation of several PPAR isoforms, downregulation of LXR and cholesterol accumulation, changes in n3/n6 polyunsaturated fatty acid ratio, activation of lipoxygenases, soluble epoxide hydrolase, acid sphingomyelinase and their products. Mitochondrial damage and ensuing oxidative stress and inflammation are well known contributors to the pathogenesis of DR. Recent studies identified several classes of non-coding RNAs, including microRNAs, long noncoding RNAs, and circular RNAs to be involved in retinal vascular damage in DR. Although DR is a microvascular disease with clinical manifestations based on vascular pathology, the molecular mechanisms leading to DR pathogenesis involve multiple retinal cells. Muller cells, pericytes and microglia are well known players in DR pathogenesis. Ganglion cells, photoreceptors and RPE cells were shown to significantly contribute inflammatory cytokines and VEGF production in diabetic retina. This presentation will give an overview of hyperglycemia and dyslipidemia-induced molecular mechanisms leading to the development and progression of DR.		
10:35-11am	The Gut-Eye Axis	**Maria B. Grant, MD, FARVO**, University of Alabama at Birmingham, Birmingham, AL Grant MB and microbiome and diabetic retinopathy - Search Results - PubMed (nih.gov)
Recent studies support the existence of a gut-retina axis involved in the pathogenesis of several chronic progressive ocular diseases, including diabetic retinopathy and age-related macular disorders. This presentation aims to underline the importance of the gut microbiome in relation to ocular health. Characteristics of the gut microbiome in terms of composition and function and the role of gut microbiome dysbiosis in the pathogenesis of diabetic retinopathy will be discussed. The presentation will also address the critical role of the renin angiotensin systems (RAS) characterized by decreased systemic and tissue angiotensin-converting enzyme 2 (ACE2) expression, specifically intestinal ACE2. To evaluate intestinal barrier integrity, T1D subjects with (n=18) and without (n=20) retinopathy and age-matched healthy controls (n=34) were examined for changes in key gut-regulated components of the immune system, the gut leakage marker fatty acid binding protein 2 (FABP2), the gut microbial antigen peptidoglycan (PGN), and angiotensin II (Ang II), the primary effector of the deleterious RAS. T1D subjects exhibit alterations in gut derived circulating immune cells with increased abundance of Th17 and ILC1 cells compared to controls; gut permeability markers, FABP2 and PGN, directly correlated with plasma Ang II and increased with diabetic retinopathy severity (Prasad R et al Cir Res 2023). To further interrogate the role of intestinal ACE2, we performed studies in Akita >mice. Intestinal ACE2 is markedly reduced in these mice and three approaches were utilized to prevent diabetes-induced loss of intestinal ACE2: oral administration of a Lactobacillus paracasei (LP) probiotic in which the humanized ACE2 protein (LP-ACE2) is expressed and secreted into the intestinal lumen. In the LP-ACE2 cohort, gut barrier integrity was increased and the number of retinal acellular capillaries were reduced. Taken together, our study demonstrates that dysregulated systemic and intestinal RAS is associated with worsening		

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gut barrier permeability, gut-derived immune cell activation, systemic endotoxemia, and progression of diabetic retinopathy in human subjects. In Akita mice, use of LP-ACE2 decreased gut barrier leakage and histologic features of diabetic retinopathy. These highly novel findings emphasize the multi-faceted role of the intestinal RAS in diabetes and diabetic retinopathy and the key role of the gut-retina axis.		
11-11:25am	Illuminating the dark matter: non-coding RNAs in diabetic retinopathy	**Subrata Chakrabarti, MD, PhD** Western University, London, ON, Canada chakrabarti s and non coding rnas and diabetic retinopathy - Search Results - PubMed (nih.gov)
Glucose induced endothelial damage and dysfunction is a key factor for the development of diabetic retinopathy. Endothelial dysfunction induces cellular phenotypic changes, characterized by decreased expression of endothelial cell markers and functions, together with increased expression of mesenchymal markers and functions i.e, endothelial to mesenchymal transition (EndMT). In the retina such changes pave the pathway to vascular structural and functional alterations and neovascularization. Gene expression at the transcription and at the post transcriptional levels are regulated by several epigenetic mechanisms. Such mechanisms include histone modification, such as acetylation/deacetylation, ubiquitination, methylation, DNA methylation and regulatory activities mediated through non-coding RNAs. There are several non-coding RNAs (ncRNAs). The list includes microRNAs (miRNA), long non-coding RNAs (lncRNAs), circular RNAs (circRNAs) tRNAs, rRNAs, small nuclear RNAs (snRNAs), PIWI-interacting RNAs (piRNAs), small nucleolar RNAs (snoRNAs) etc. There are various modes of action of these molecules as they work at various levels of transcription. The role of the ncRNAs, once called `dark matter of the genome' have started to unravel. Although the whole area is relatively new, this session will focus on some of the better studied ncRNA (miRNAs, lncRNAs, circRNAs) in the context of diabetic retinopathy. Studies in ncRNA have uncovered novel pathogenetic mechanisms in diabetic retinopathy. Decoding such processes may lead to development of novel RNA based approaches for the diagnosis and treatment of diabetic retinopathy.		
11:25-11:50am	Mitochondrial Epigenetics in Diabetic Retinopathy	**Renu Kowluru, PhD** **Wayne State University, Detroit, MI** **Kowluru R and mitochondriaand diabetic retinopathy - Search Results - PubMed (nih.gov)**
Diabetic retinopathy is a multifactorial disease, and the exact mechanism of its development remains elusive. Mitochondrial dysfunction is considered to play a major role in the pathogenesis of this blinding disease. This presentation will focus on the role of epigenetic modifications, modifications that can alter expression of a gene without making any change in the DNA sequence, in mitochondrial homeostasis. Latest information about damage to the mitochondrial genomic and functional stability will be discussed including the role of mitochondrial genome-encoded long noncoding RNAs.		
11:50-12pm	Discussion	
12-1pm	Lunch	

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1:00-1:25pm	Neuronal dysfunction in diabetic retinopathy	**Elliott Sohn, PhD, University of Iowa, Iowa City, IA** Sohn E and diabetic retinopathy - Search Results - PubMed (nih.gov)
Diabetes mellitus results in microvascular damage and ischemia in addition to neuronal degeneration in animal models and humans. Diabetic retinal neuropathy (DRN) is gaining recognition as a feature of diabetic retinal disease that can occur before traditional signs of 'diabetic retinopathy' are observed. This presentation will examine evidence and the importance of DRN in the context of the neurovascular unit, and how this may impact vision loss from diabetic retinal disease.		
1:25-1:50pm	Role of Choroid in Diabetic Retinopathy-Current Status	**Tomoaki Murakami, MD, PhD**
The choroid serves as the supplier of oxygen and nutrients to the outer retinas, mediated via retinal pigment epithelium (RPE), and regulates inflammatory responses in the pathological states. Retinal vascular lesions have been well defined in diabetic retinopathy (DR), whereas the characterization of diabetic choroidopathy should be achieved. The advances in both basic and clinical investigation are now elucidating the multifaceted aspects of the choroid in diabetic patients; the pathohistology, molecular mechanisms, and clinical imaging. Histological studies had revealed the pathological changes in choroidal vessels, e.g., the degeneration of choriocapillaris, tortuous choroidal vessels, referred as to 'diabetic choroidopathy'. Leukocyte-endothelial interaction might contribute to the capillary obstruction as well as inflammatory responses. These findings suggest the great contribution to the pathogenesis in DR, although we cannot easily find the clinical findings specific to diabetic choroidopathy. Basic research has elucidated that VEGF derived from the RPE guarantees vascular homeostasis and contributes to the hyperpermeability in the choriocapillaris. Resident and circulating leukocytes promote inflammatory responses and obstruction of choroidal vessels, mediated via several cytokines, e.g., TNF, IL1b, and ICAM. Recent development of single cell analysis of transcriptome may allow us to understand the differences in the molecular mechanisms between the macular and peripheral choroid. Advances in the imaging modalities, e.g., OCT, OCT angiography (OCTA), and fundus autofluorescence, have promoted our understanding of in vivo structure of the choroid in diabetic patients. Structural OCT delineates the reduced vascular density and vascular tortuosity in the Sattler's and Haller's layers. OCTA clinically reveals the flow void in the choriocapillaris layer as the DR progresses. Hyperreflective foci on OCTA images might correspond to lipid-laden macrophages and represent inflammatory responses. Future analyses using widefield imaging should promote the comparative studies between the macular and peripheral areas. These results would improve our understanding of how the choroid plays an important role in the visual impairment in diabetic patients.		
1:50-2:15pm	Autonomous AI for Diabetic Retinopathy: From algorithm through ethics to health equity	**Michael David Abramoff, MD, PhD, FARVO,** University of Iowa, Iowa City, IA Abramoff MD and artificial intelligence - Search Results - PubMed (nih.gov)
The diabetic retinopathy field forward is already moving forward thanks to advances, such as autonomous AI, through consideration of all stakeholders in healthcare. The presentation will look at all stakeholders such as regulators...		

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2:15-2:40pm	Novel imaging approaches	**Caroline R. Baumal, FRCSC, MD**, New England Eye Center, Tufts University, Boston, MA Baumal CR and imaging - Search Results - PubMed (nih.gov)
Retinal imaging plays a key role in diagnosis, staging of severity and treatment of diabetic retinopathy. Updates on classical imaging modalities such as fundus photography, optical coherence tomography and fluorecein angiography will be reviewed. Novel imaging with OCT angiography, widefield imaging, and imaging biomarkers used to evaluate diaetic retinopathy disease severity will be explored.		
2:40-2:50pm	Discussion	
2:50-3:05pm	Afternoon Break	
3:05-3:30pm	Vascular regeneration as an exciting concept for diabetic retinopathy	**Alan Stitt, PhD** Queens University, Belfast, UK Cellular therapy and Stitt A and diabetic retinopathy - Search Results - PubMed (nih.gov)
This presentation will explore how pathogenic changes to cell: cell interactions within the retinal neurovascular unit (NVU) provide an important focal point for fully understanding neurovascular pathology in the context of diabetic retinopathy. Clinical evidence combined with animal model data from a range of molecular cell biology perspectives will be discussed. In particular, the potential of single cell profiling backed up supporting pathophysiological data will be shown. Also, the known shared pathophysiology between the NVU in the brain and retina during diabetes with be presented to help explain possibilities for shared molecular pathways between cognitive decline, dementia and the characteristic neuroglial and vascular pathology associated with diabetic retinopathy. Understanding these common pathways and the degree to which they occur simultaneously in the brain and retina, especially during Type 2 diabetes will offer interesting angles, not only on how we assess and treat diabetic retinopathy but how the retina could be a useful window into the brain.		
3:30-355pm	Anti-VEGF therapy in diabetic retinopathy - Current status	**Lloyd P. Aiello, MD, PhD, FARVO,** Joslin Diabetes Center, Boston, MA Aiello LP and VEGF - Search Results - PubMed (nih.gov)
The field of anti-VEGF therapy for Diabetic Retinopathy continues to evolve with new interventional agents, novel delivery approaches, and revised treatment algorithms. Extensive efforts are also being made to find biomarkers and other methods to predict progression, the need for treatment and to monitor treatment response. This presentation will update the current status of this field.		
3:55-4:20pm	Laser Therapy/surgery	**Rajendra S. Apte, MD, PhD** University of Washington, St. Louis, MO APte RS and laser - Search Results - PubMed (nih.gov)

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Current paradigms in research into and treatment of diabetic retinopathy will be discussed.		
4:20-4:25pm	Discussion	
4:25-4:30pm	Summary	**Arup Das, MD, PhD**, University of New Mexico Das A and diabetic retinopathy - Search Results - PubMed (nih.gov)
4:30pm	Adjourn	