Diabetic retinopathy: Moving the field forward

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

Description
Despite tremendous progress in developments of treatment, the management of diabetic macular edema and proliferative diabetic retinopathy remains challenging. The current anti-VEGF therapies are not optimal as many patients respond poorly with this treatment. Clinician-scientists must be up to date regarding the management of these patients with newer pharmacotherapy protocols based on results of recently finished, multi-center clinical trials and the use of new diagnostic tools.

In this course, clinicians and basic scientists in the field will address various aspects of diabetic retinopathy including how to set up a clinical trial, genetic associations and novel single-cell technology and imaging techniques. The course will provide an outstanding platform for the vision community for a balanced discussion of the experimental and clinical aspects of diabetic retinopathy.

Learning objectives
After attending this course, participants will be able to:

- Review the clinical aspects, epidemiology, systemic factors and genetics of diabetic retinopathy.
- Describe the new experimental models, molecular mechanism and role of various retinal cell types.
- Identify the role of inflammation, mitochondria damage and microRNAs in diabetic retinopathy.
- Evaluate the major, ongoing clinical trials on therapies in diabetic retinopathy.
- Describe the novel therapies including pharmacotherapies.
- Summarize the diagnostic studies, novel biomarkers and utilization of artificial intelligence in diabetic retinopathy.

Agenda
Presenters and presentations may change.

8 – 8:05am  Introduction and welcome
Renu A. Kowluru, PhD, FARVO, Kresge Eye Institute, Wayne State University, Detroit, MI

Education course ‘Diabetic Retinopathy: Moving the Field Forward’ will provide a comprehensive overview of the genetic factors, basic mechanisms, experimental models, clinical manifestation, biomarkers and novel pharmacotherapies. The discussion will also focus on the ongoing clinical trials and how artificial intelligence can be utilized. Overall, we will strive to provide a platform for a balanced discussion covering major basic science and clinical issues important in diabetic retinopathy field.
Clinical overview of diabetic retinopathy

Arup Das, MD, PhD, University of New Mexico School of Medicine, NM VA Health Care System, Albuquerque, NM

The recent classification of different stages of diabetic retinopathy, the pathophysiology of the clinical features, the current imaging, and treatment modalities including laser, pharmacotherapy and surgery will be summarized to give an introduction to the course.

Epidemiology and systemic risk factors

Tien Y. Wong, FRCS, PhD, FARVO, Singapore National Eye Centre, Singapore

Diabetic retinopathy (DR) is the most specific microvascular complication of diabetes, and the leading cause of blindness among working adult people, estimated to affect more than 100 million worldwide. In the past few decades, there have been a range of large population-based epidemiological studies that have provided new information on the global prevalence of diabetic retinopathy and its risk factors.

First, epidemiological studies suggest that there are approximately 93 million people with retinopathy worldwide, with 17 million with proliferative retinopathy and 21 million with diabetic macular edema. There is also increasing evidence that there is decline in the incidence of blindness due to DR, particularly in Western/developed countries, so the public health challenge is shifting to newly developed countries.

Second, diabetic macular edema (DME) rather than proliferative retinopathy (PDR) is the increasingly common cause of vision impairment. Third, there is a better understanding of the relationship of diabetic retinopathy to the three major modifiable risk factors – namely hyperglycemia, hypertension and dyslipidemia.

Third, DR awareness remains patchy and low in most populations. Fourth, of the major risk factors, hyperglycemia remains the most consistent risk factor for DR in type 1 diabetes across different studies and populations. In contrast, blood pressure is an important risk factor for DR in type 2 diabetes, while the relationship of dyslipidemia and DR remains unclear, with inconsistent results from different studies and trials.

Finally, photographic screening of DR using tele-ophthalmology platforms is increasingly recognized as being feasible and cost-effective, but DR screening and prevention in low-resource settings cannot follow models developed in high-resource countries and requires different strategies.

The multifaceted genetic architecture of diabetic retinopathy

Sudha K. Iyengar, PhD, Case Western Reserve University, Cleveland, OH

Diabetic retinopathy (DR) is a major cause of adult blindness globally. Salient factors in risk of DR are poor glycemic control and duration of diabetes, but these factors show a multifaceted profile in various populations. Dr. Iyengar will present up-to-date information on various cohorts being analyzed to discover genes for diabetic retinopathy, and where the field needs to go. Dr. Iyengar has worked on diabetic complications for much of her career, participating in the Lasker Foundation and International Retinal Research Foundation's initiative on Diabetic Retinopathy from 2012-2018.
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

This presentation will describe the available animal models that may be used to study various aspects of diabetic retinopathy. A number of different procedures and genetic approaches have been developed that recapitulate various aspects of diabetes and diabetic retinopathy specifically. The emphasis of this class will be on understanding the specific features of diabetic retinopathy represented in these animal models and discuss relative strengths and weaknesses.

9:45 – 9:55am  Discussion

9:55 – 10:10am  Morning Break

10:10 – 10:35am  Molecular Mechanism in the pathogenesis of diabetic retinopathy

Maria B. Grant, MD, FARVO, University of Alabama at Birmingham, Birmingham, AL

This presentation focuses on the basic mechanisms responsible for the pathogenesis of diabetic retinopathy. Diabetes represents a global epidemic with 425 million people affected (2017) and projected to rise to 629 million in 2045 (WHO report). Diabetes is projected to rise to 33% of the US population by 2050 (Boyle JP 2010). While the histological features, capillary and glial changes, are well described, the mechanism leading to these changes and the temporal sequence of their development remain incompletely understood. The role of hyperglycemia and the implications of the Diabetes Control and Complications Trial (DCCT) will be discussed. The implications of hyperlipidemia and the significance of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial considered. The implications of biochemical mechanisms such as Advanced Glycation End-Products (AGEs) and protein kinase C (PKC) and hormonal contributions (growth hormone/IGF-1) will be describe from both a current and historical perspective. The concept of vascular repair and how diabetes hinders this critical physiological process will be explained in detail. The potential contributions of neuronal changes to diabetic retinopathy and “Neuroprotection” as a therapeutic strategy for diabetic retinopathy will be outlined. Finally, a new area is the role of the gut microbiome in the pathogenesis retinopathy. Strategies to manipulate the gut microbiome and the gut intestinal barriers to prevent metabolic endotoxemia and retinopathy will be considered.

10:35 – 11am  Mitochondrial dysfunction in diabetic retinopathy

Renu A. Kowluru, PhD, FARVO, Kresge Eye Institute, Wayne State University, Detroit, MI

Mitochondria occupy a central place in the development of diabetic complications including retinopathy, and their homeostasis is critical for keeping the retina and its vasculature healthy. This presentation will discuss how mitochondrial maintains its homeostasis, why they become dysfunctional in diabetes, and how dysfunctional mitochondria contribute to the development of diabetic retinopathy. Discussion will also focus on the strategies to maintain mitochondrial homeostasis.
Retinal vascular inflammation in diabetic retinopathy

John S. Penn, PhD, FARVO, Vanderbilt University School of Medicine, Nashville, TN

Clinical trials have concluded that effective control of blood sugar delays the onset of pathology and also that lipid lowering drugs (e.g., fenofibrate/simvastatin) retard progression, which argues that both hyperglycemia and dyslipidemia can promote retinopathy in diabetics. In NPDR, hyperglycemia and dyslipidemia contribute to chronic, progressive inflammation that results in retinal pathology through, as yet, largely undefined mechanisms. However, accumulating experimental evidence points to involvement of pro-inflammatory cytokines. Several retinal cell types, including Muller glia, endothelial cells (EC) and pericytes, secrete soluble pro-inflammatory cytokines (e.g., TNFα, IL-1β, IL-6, IL-8) in response to high glucose or elevated free fatty acids. In animal models and patients, increased retinal or vitreous levels of these cytokines are observed early in DR progression. These mediators are experimentally linked to increased adhesion of leukocytes to the lumen of the retinal endothelium, or leukostasis. Adhered leukocytes can occlude capillaries leading to downstream ischemia and can release pro apoptotic factors leading to pericyte death. Recent findings suggest that increases in retinal pro inflammatory cytokines in NPDR also directly trigger pericyte apoptosis. These events compromise vascular integrity and promote the transition to vision-threatening pathology. As there are currently no therapeutic strategies directed at early stage NPDR, new therapies targeting inflammation could offer an effective alternative to current approaches. This presentation will consider the role of chronic retinal inflammation in the onset and progression of diabetic retinopathy and will examine the therapeutic potential of anti-inflammatory strategies.

Update on imaging in diabetic retinopathy

Caroline R. Baumal, FRCSC, MD, New England Eye Center, Tufts University, Boston, MA

Imaging of the posterior pole plays a key role in diagnosis, classification and management of diabetic retinopathy (DR). New imaging techniques are continually being introduced while established ones are improved. Widefield fundus photography and fluorescein angiography, as well as multimodal imaging have enhanced diagnosis of DR severity. OCT angiography provides detailed information about retinal and choroidal vasculature in DR. Subtle abnormalities may be imaged with OCT of the retinal nerve fiber layer (RNFL) as well as with OCT angiography prior to clinically visible retinopathy. Technological advances have improved image acquisition, processing, reproducibility and comparability between sequential retinal examinations. The current imaging techniques used to evaluate structural and functional changes in DR will be reviewed.

The role of neuronal dysfunction in diabetic retinopathy

Machelle T. Pardue, PhD, Atlanta VA Medical Center, Georgia Institute of Technology, Emory University, Decatur, GA

Current clinical methods to detect and treat diabetic retinopathy focus on vascular changes that occur 10-15 years after diabetes onset. However, neuronal dysfunction has been identified prior to the clinically-recognized vascular changes. Our research has focused on
developing methods for early detection of neuronal dysfunction using electroretinogram (ERG) changes. We have identified delays in the inner retinal response generating the ERG oscillatory potentials (OP) using dim flash stimuli. These OP delays are detectable prior to vascular changes in diabetic rodents and patients with diabetes. Since dim flash stimuli generate rod photoreceptor-dominated responses, it appears that retinal rod pathways are most sensitive to diabetic insult. Furthermore, treatment with levodopa slows the progression of these neuronal defects in rodents when given chronically and reverses the OP delays in patients with diabetes when given acutely.

1:25 – 1:50pm  
**Exosomes in diabetic retinopathy**  
*Julia Busik, PhD, Michigan State University, East Lansing, MI*

Diabetic retinopathy (DR) is a sight-threatening microvascular complication of diabetes. Recent studies have demonstrated that exosomes, small vesicles that are secreted into the extracellular environment, can participate in causing the vascular damage associated with DR. Exosomes have a cargo of miRNAs, lipids, and proteins, including complement proteins in plasma. This presentation will discuss the role of exosomes and different components of exosomal cargo in the development and progression of DR.

1:50 – 2:15pm  
**Biomarkers of diabetic retinopathy**  
*Sayon Roy, PhD, FARVO, Boston University School of Medicine, Boston, MA*

The prevalence of diabetic retinopathy (DR), the leading cause of blindness in working-age adults, has been steadily increasing that reflects the global diabetes epidemic. The International Diabetes Federation reports that if this trend continues then by 2035 the diabetic population would reach 592 million worldwide. Therefore, developing strategies for identifying patients at risk of diabetic complications including DR, are of urgently needed. DR is the most frequent complication of diabetes driven by various biochemical and structural changes affecting the neurovascular components of the retina. To optimize therapy, biomarkers could be of significant value in identifying diabetic individuals at risk of developing DR or progressing to advanced DR. Biomarkers provide a better understanding of the development and progression of the disease status and thereby facilitate optimized treatment. While biomarkers for DR are primarily based on pathogenic mechanism underlying the development and progression of DR involving increased vascular permeability, elevated levels of inflammatory proteins in serum and ocular biofluids, increased levels of AGEs, oxidative stress, endothelial dysfunction, proangiogenic factors and others, recent advancements in retinal imaging are also promising and could serve as novel biomarkers for DR that could contribute to increased detection and treatment of DR patients. This presentation will focus on the latest updates on specific biomarkers relevant to DR.

2:15 – 2:40pm  
**MicroRNAs network in diabetic retinopathy**  
*Manuela Bartoli, PhD, Augusta University, Augusta, GA*

Epigenetic regulation of gene expression involving non-coding RNAs has recently emerged as an important contributor to the pathogenesis of diabetic retinopathy (DR). RNA arrays and targeted analysis have evidenced the occurrence of profound changes in the expression pattern of a large number of microRNAs (miRs). These changes were confirmed in human and experimental DR, prompting further analysis demonstrating the relevance of specific miRs to DR induction and progression. Most analyzed miRs in DR revealed their impact on oxidative stress, vascular senescence and inflammation. Whether or not these miRs could
represent potential DR biomarkers or therapeutic targets remains to be confirmed and could be complicated by the existence of an intricate regulatory network of miRs expression and function involving their interaction with other miRs, other non-coding RNAs and regulatory proteins.

2:40 – 2:50pm Discussion

2:50 – 3:05pm Afternoon break

3:05 – 3:30pm Artificial intelligence for diabetic retinopathy

*Michael David Abramoff, MD, PhD, FARVO, University of Iowa Hospitals & Clinics, Iowa City, IA*

Autonomous Artificial Intelligence (AI) describes systems capable of making decisions of high cognitive complexity. For example, a diagnostic autonomous AI system for the point of care diagnosis of diabetic retinopathy, which provides a direct diagnostic recommendation without physician interpretation, performs a task otherwise reserved for ophthalmologists and optometrists, who only make up 0.02% of the US population, and have extensive, specialized, training and experience. Such rigorously validated medical diagnostic AI systems hold great promise for improving access to care, increasing accuracy, and lowering cost, while enabling specialist physicians to provide the greatest value by managing and treating patients whose outcomes can be improved. Ensuring that autonomous AI provides these benefits requires negotiating several ethical and practical challenges. Recently, the first autonomous point of care diabetic retinopathy exam was *de novo* authorized by the US FDA, after a preregistered clinical trial. Because no prior approval could serve as guidance, and because of the significant ethical and legal concerns raised around introducing autonomous AI into healthcare,(4) we will describe these concerns, go through the ethical principles we drew on, and explain how we practically addressed them through the design, clinical trial and during ongoing implementation.

3:30 – 3:55pm Anti-VEGF therapy in diabetic retinopathy - current status

*Lloyd P. Aiello, MD, PhD, FARVO, Joslin Diabetes Center, Boston, MA*

The advent of VEGF inhibitors revolutionized the care of patients with diabetic macular edema, age-related macular degeneration, retinal vein occlusion and other ischemic retinopathies. Evolving data in diabetic eye disease have shown benefit for proliferative diabetic retinopathy and diabetic retinopathy severity as well. The clinical benefit in different patient cohorts and therapeutic differences between various VEGF inhibitors have also been evaluated. This presentation will present the latest data on the indications, use and efficacy of various anti-VEGF therapies for the treatment of diabetic macular edema, proliferative diabetic retinopathy and diabetic retinopathy severity.

3:55 – 4:20pm Novel pharmacotherapies in development for diabetic retinopathy and diabetic macular edema

*Quan Dong Nguyen, MD, MSc, Stanford University, Palo Alto, CA*

The management of diabetic macular edema (DME) and diabetic retinopathy (DR) has been revolutionized by the development of anti-VEGF therapy. Gain in visual acuity can now be acquired in eyes with DME. Regression and improvement of diabetic retinopathy severity scale (DRSS) can also be achieved. However, the burden of frequency of treatments coupled
with the suboptimal percentage of patients who gain significant vision or who may depend on therapies chronically have led to further investigations into other approaches to manage DME and DR.

The presentation will focus on novel pathways that may be involved in the pathogenesis of DME and DR such as cell signaling, receptor activation, and inflammation with interleukins and adhesion molecules. Mechanisms to antagonize such pathways will be discussed along with specific inhibitors and approaches that are currently being investigated in clinical trials for patients with DME and/or DR.

4:20 – 4:25pm Discussion

4:25 – 4:30pm Summary

*Arup Das, MD, PhD, University of New Mexico School of Medicine, NM VA Health Care System*

General recap of the day.