DIABETIC RETINOPATHY: PAST, PRESENT AND FUTURE

Organizers: Renu A. Kowluru, PhD, FARVO and Arup Das, MD, PhD, FARVO

Diabetes is a global epidemic afflicting approximately 400 million people, and retinopathy is one of its most feared complications, which affects over 90% of patients after 25 years of diabetes. The course will cover various aspects of diabetic retinopathy, including genetic associations and systemic factors, and will highlight cellular targets, novel imaging techniques and future therapies. The course will provide an outstanding platform for the vision community for a balanced discussion of the experimental and clinical aspects of diabetic retinopathy.

8:30-8:40am
Welcome and introduction
Renu A. Kowluru, PhD, FARVO, Kresge Eye Institute, Wayne State University School of Medicine

We have an exciting course covering various features of diabetic retinopathy including genetic associations, systemic factors, novel imaging techniques and future therapies. We hope to provide an outstanding platform for a balanced discussion of the experimental and clinical aspects of diabetic retinopathy.

8:40-9:05am
Clinical Overview of Diabetic Retinopathy
Arup Das, MD, PhD, FARVO, UNM Eye Center, University of New Mexico School of Medicine

The clinical features of different stages of diabetic retinopathy, non-proliferative and proliferative will be described along with the histological and functional changes in the retinal tissue. Also, an update on the current management outline will be presented to give an introduction to the subject.

9:05-9:30am
Epidemiology of Diabetic Retinopathy
Tien Yin Wong, FRCS, PhD, FARVO, Singapore National Eye Centre

Diabetic retinopathy (DR) is a specific microvascular complication of diabetes, and the leading cause of blindness among working adult people worldwide. Over the past decade, there have been developments in understanding the epidemiology and trends in diabetic retinopathy. First, there is clear evidence of a global increase in the prevalence of diabetes, although there is a decline in the incidence of blindness due to DR, particularly in developed countries. Second, diabetic macular edema (DME) rather than proliferative retinopathy (PDR) is the increasingly common cause of vision impairment. DME is now known to affect around 6.8% of the diabetic population. 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. This lecture will cover new understanding of the epidemiology, risk factors and trends in the epidemiology of diabetic retinopathy, with insights from studies across different diverse populations.
9:30-9:55am  
**Systemic Factors Associated with Diabetic Retinopathy**  
Emily Chew, MD, FARVO, National Eye Institute

**PURPOSE:** To evaluate the systemic risk factors associated with diabetic retinopathy.  
**METHODS:** Evaluation of several systemic factors from epidemiologic studies as well as randomized clinical trials demonstrate the importance of intensive glycemic control, blood pressure control, and management of serum dyslipidemia. Dietary risk factors were also evaluated in a randomized controlled clinical trial of Mediterranean diet. The observational data on fish consumption was also evaluated in this clinical trial.  
**RESULTS:** In both types 1 and 2 diabetes, intensive glycemic control resulted in beneficial effects when compared with standard glycemic control. The “legacy effect” or “metabolic memory” defined as the persistence of the beneficial effects of intensive glycemic control following the end of a clinical trial is intriguing and is found in both types 1 and 2 diabetes. Intensive glycemic control also resulted in beneficial effects on nephropathy and neuropathy associated with diabetes. Early studies of blood pressure control showed an important effect on diabetic retinopathy and other diabetic microvascular complications. Dyslipidemia was associated with increased risk of macular edema as well as proliferative diabetic retinopathy. Treatment of dyslipidemia with fenofibrate, a drug designed to decrease serum triglyceride levels and to increase the high density lipoprotein (HDL) cholesterol was found to reduce the risk of diabetic retinopathy progression by about one-third in two independent randomized controlled clinical trials. Dietary intake may also be associated with progression of diabetic retinopathy. Randomized clinical trials showed that diets enriched with extra-virgin olive oil and nuts have a reduced risk of progression of diabetic retinopathy to require treatment. Observational data found an association of increased fish intake with reduced progression of diabetic retinopathy.  
**CONCLUSIONS:** System risk factors play important roles in the progression of diabetic retinopathy. The results from various landmark studies of diabetes support the importance of intensive glycemic control, intensive blood pressure control, and management of dyslipidemia, especially with fenofibrate. Dietary intake may also be associated with progression of diabetic retinopathy. It is important to conduct further studies in this area of association of nutrition and diabetic retinopathy.

9:55-10:05am – Discussion  
10:05-10:20am – Break

10:20-10:45am  
**Update on the Genetics of Diabetic Retinopathy**  
Lucia Sobrin, MD, MPH, Massachusetts Eye and Ear

Diabetic retinopathy (DR) is a polygenic disorder. Twin studies and familial aggregation studies have documented clear familial clustering. Heritability has been estimated to be as high as 27% for any DR and 52% for proliferative diabetic retinopathy (PDR), an advanced form of the disease. Results from linkage analyses, candidate gene association studies and genome-wide association studies (GWAS) performed to date will be reviewed. Combined analysis of the data from multiple GWAS is emerging as an important next step to explain the unaccounted heritability. Key factors to future discovery of the genetic underpinnings of DR are precise DR ascertainment, a focus on the more heritable disease forms such as PDR, stringent selection of control participants with regards to duration of diabetes, and methods that allow combination of existing datasets from different ethnicities to achieve sufficient sample sizes to detect variants with modest effect sizes.

10:45-11:10am  
**Resistance of Diabetic Retinopathy to Arrest its Progression after Termination of Hyperglycemia- Metabolic Memory & Epigenetics**  
Renu A. Kowluru, PhD, FARVO, Kresge Eye Institute, Wayne State University School of Medicine

Progression of retinopathy in diabetic patients resists arrest even after re-institution of tight glycemic control, suggesting a metabolic memory phenomenon. Recent studies have shown that stable and heritable covalent modifications, caused by external factors and/or disease state, can affect gene transcription, and these epigenetic modifications do not alter the base sequence of the DNA. This presentation will discuss the role of epigenetics in the metabolic memory phenomenon, and will highlight possible therapeutic targets to prevent progression of this blinding disease.
Inflammation and Angiogenesis in Diabetic Retinopathy- Role of Lipid Metabolites

Lois E.H. Smith, MD, PhD, FARVO, Boston Children’s Hospital

Diabetic retinopathy and macular edema are major causes of blindness. Fenofibrate treatment in type 2 diabetes patients reduces progression of diabetic retinopathy and CME independent of its peroxisome proliferator-activated receptor (PPAR)α agonist lipid lowering effect. The mechanism is unknown. Fenofibrate binds to and inhibits cytochrome P450 epoxygenase (CYP)2C with higher affinity than to PPARα. CYP2C metabolizes ω-3 long-chain polyunsaturated fatty acids (LCPUFAs). While ω-3 LCPUFA products from other metabolizing pathways decrease retinal and choroidal neovascularization, CYP2C products of both ω-3 and ω-6 LCPUFAs promote angiogenesis. We found that fenofibrate inhibits retinopathy by reducing CYP2C ω-3 LCPUFA (and ω-6 LCPUFA) pro-angiogenic metabolites. Fenofibrate reduces retinal and choroidal neovascularization in PPARα-/- mice and augments ω-3 LCPUFA protection via CYP2C inhibition. Fenofibrate suppresses retinal and choroidal neovascularization in mice overexpressing human CYP2C8 in endothelial cells and reduced plasma levels of the pro-angiogenic ω-3 LCPUFA CYP2C8 product, 19,20-epoxydocosapentaenoic acid. 19,20-epoxydocosapentaenoic acid reversed fenofibrate-induced suppression of angiogenesis ex vivo and suppression of endothelial cell functions in vitro. In summary fenofibrate suppresses retinal and choroidal neovascularization via CYP2C inhibition as well as by acting as an agonist of PPARα. Fenofibrate augments the overall protective effects of ω-3 LCPUFAs on diabetic eye diseases.

11:35-11:50am - Discussion
11:50am-12:50pm - Lunch

12:50-1:15pm
Basic Science of Diabetic Retinopathy
Timothy S. Kern, PhD, FARVO, Case Western Reserve University School of Medicine

Numerous molecular alterations that occur in the retina have been identified in diabetic animals and patients, and this information has allowed identification of potential therapeutic targets to inhibit diabetic retinopathy. In vivo tests, largely conducted in animals, show some benefit on the few endpoints assessed, but evidence indicates that the individual therapies do not restore the molecular environment of the the retina to "normal". A new approach to inhibiting diabetic retinopathy attempts to therapeutically restore the entire retina in diabetes as close to normal as possible.

1:15-1:40pm
Cellular Targets of Diabetic Retinopathy
Sayon Roy, PhD, FARVO, Boston University School of Medicine

An overwhelming cause of vision loss in diabetic individuals is the breakdown of retinal vascular homeostasis, contributing to excess permeability and the development of macular edema, a prominent clinical manifestation of diabetic retinopathy. Recent studies have begun to shed light on molecular targets that not only compromises the BRB characteristics but also affects vascular homeostasis and promotes cell loss associated with the development and progression of diabetic retinopathy. Our research has identified key targets including basement membrane (BM) genes, fibronectin, collagen IV, and laminin that are abnormally expressed under hyperglycemic condition and contribute to abnormal cell- cell communication and retinal vascular leakage. A strategy for decreasing BM thickening, vascular leakage and maintenance of vascular homeostasis in the diabetic retina will be the topic of this presentation.

1:40-2:05pm
Novel Biomarkers in Diabetic Retinopathy - Their Role in Clinical Practice and in Research
Alicia Jenkins, MBBS, MRCP, MD, FRACP, FRCP, NHMRC Clinical Trials Centre, University of Sydney

There are multiple risk factors and markers for the onset and progression of diabetic retinopathy, yet residual risk remains. Screening for diabetic retinopathy is recommended to facilitate early detection and treatment. Common biomarkers of diabetic retinopathy and its risk in clinical practice today relate to the visualization of the retinal vasculature and measures of glycemia, lipids, blood pressure, body weight, smoking, and pregnancy status. Greater knowledge of novel biomarkers and mediators of diabetic retinopathy, such as those related to inflammation and angiogenesis, has contributed to the development of
additional therapeutics, in particular for late-stage retinopathy, including intra-ocular corticosteroids and intravitreal vascular endothelial growth factor inhibitors ('anti-VEGFs') agents. Unfortunately, in spite of a range of treatments (including laser photocoagulation, intraocular steroids, and anti-VEGF agents, and more recently oral fenofibrate, a PPAR-alpha agonist lipid-lowering drug), many patients with diabetic retinopathy do not respond well to current therapeutics. Therefore, more effective treatments for diabetic retinopathy are necessary. New analytical techniques, in particular those related to molecular markers, are accelerating progress in diabetic retinopathy research. Given the increasing incidence and prevalence of diabetes, and the limited capacity of healthcare systems to screen and treat diabetic retinopathy, there is need to reliably identify and triage people with diabetes. Biomarkers may facilitate a better understanding of diabetic retinopathy, and contribute to the development of novel treatments and new clinical strategies to prevent vision loss in people with diabetes. The presentation will review key aspects related to biomarker research, including some specific diabetic retinopathy-relevant clinical, biochemical and molecular biomarkers, in both ocular and extraocular sites.

2:05-2:30pm
In vivo Retinal Imaging for Diabetic Retinopathy: New Perspective of a Known Entity
Susanna S. Park, MD, PhD, UC Davis Eye Center

This is an overview of the new advances in vivo retinal imaging that have provided new insights to our understanding of the pathogenesis of diabetic retinopathy. Ultra-wide field fundus photography and fluorescein angiography have shown that changes associated with diabetic retinopathy extend beyond the 7-standard ETDRS fundus fields traditionally used to grade the severity of retinopathy. Studies are being conducted to evaluate the role of the peripheral retinal pathology in progression of diabetic retinopathy. Optical coherence tomography has become an indispensable tool in diagnosing and managing patients with diabetic macular edema. With the advent of OCT angiography, retinal flow can be visualized in 3-dimensions. Subtle regional flow changes can now be evaluated and quantitated in more detail non-invasively, allowing a more accurate assessment of retinal ischemia in diabetic retinopathy. Adaptive optics imaging has detected cellular changes in the retinal photoreceptor in diabetic eyes that increase with severity of diabetic retinopathy, demonstrating that diabetic retinopathy extends beyond the inner retina. Improved visualization of the structural changes associated with diabetic retinopathy will improve our understanding of the pathogenesis of vision loss associated with diabetic retinopathy.

2:30-2:45pm- Discussion
2:45-3pm- Break

3:00-3:25pm
Anti-VEGF and Other Therapies in Clinical Diabetic Retinopathy
M. Elizabeth Hartnett, MD, FACS, FARVO, Moran Eye Center, University of Utah

Data from major clinical trials regarding inhibitors of vascular endothelial growth factor (VEGF), and some of the major studies testing corticosteroid formulations, for diabetic retinopathy and diabetic macular edema will be presented. Discussion may include new hypotheses of pathophysiology based on clinical trial information.

3:25-3:50pm
New Cellular Therapies
Maria Grant, MD, FARVO, Eugene and Marilyn Glick Eye Institute, Indiana University

In chronic diabetes, vascular reparative mechanism can be lost resulting in development of microvascular complications (MVC), such as diabetic retinopathy. This presentation will first give an overview of vascular wall and bone marrow derived reparative progenitor populations. Next how these cells are influenced by diabetes will be discussed. Bone marrow derived-vascular reparative cells circulate in the peripheral blood of healthy individuals but exist in reduce numbers in diabetic individuals. These reparative cells, CD45⁺CD34⁺ cells, were found to be dysfunctional in diabetics with MVC. Vascular wall-derived progenitor cells, called endothelial colony forming cells (ECFCs), were also found to be depleted in diabetics with MVC. Recently we studied human inducible pluripotent stem cells (hiPSCs)-derived ECFCs. These cells display the ability to form functional and durable blood vessels in vivo and conferred therapeutic revascularization by connecting with and remaining integrated with host rodent vessels long term. We characterized a mesoderm subset (SSEA5⁺KNA⁺ cells) generated from hiPSCs that gives rise to ECFCs. Finally, we used hiPSCs to generate CD45⁺CD34⁺ cells and tested the impact of co-administration of these cells with
ECFCs within the vitreous. The addition of CD34<sup>+</sup>CD45<sup>+</sup> cells with ECFCs resulted in the enhanced survival, function and reparative ability of the ECFCs. This beneficial effect was mediated by reducing retinal oxidative stress and inflammation. In summary, current interventions to foster normal vascular remodeling and restoration of blood flow to the ischemic and injured retina are limited. Our findings would support that hiPSC represent a novel tool to facilitate retinal vascular restoration and that combinations of vascular progenitors work synergistically to optimize repair.

CONTINUING MEDICAL EDUCATION (CME) AGENDA ENDS

3:50-4:15pm
Emerging Diagnostic Strategies for Diabetic Retinopathy
Ashwath Jayagopal, PhD, F. Hoffmann-La Roche Ltd.

We discuss emerging imaging technologies for early detection, disease staging, and assessment of therapeutic response in diabetic retinopathy, citing examples from OCT, adaptive optics imaging, molecular imaging contrast agents, and other technologies.

4:15-4:25pm - Discussion

4:25-4:30pm
Summary
Arup Das, MD, PhD, FARVO, UNM Eye Center, University of New Mexico School of Medicine

A summary of all the presentations will be presented at the end of the course.