ARVO EDUCATION COURSE

Saturday, April 27, 2019
8am-4:30pm
Vancouver Convention Centre
Vancouver, British Columbia, Canada

Diabetic Retinopathy: What's New

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.

8-8:05am

Introduction and Welcome

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

This exciting course will cover both clinical and basic science aspects of diabetic retinopathy. It will provide overviews of clinical pathology and molecular mechanisms/experimental models, and discuss novel areas including gut microbiome, mitochondrial epigenetics and novel targets in pipeline. We hope to provide an outstanding platform for a balanced discussion of the experimental and clinical aspects of diabetic retinopathy.

8:05-8:30am

Clinical overview of Diabetic Retinopathy

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

The clinical features, pathological correlations, diagnostic tests and current mangement of diabetic retinopathy including systemic factor control, use of anti-VEGF drugs, laser and surgery will be presented to give an overall view of the disease. This presenation will help in understanding other topics of the course that will be covered in details by individual experts in the field.

8:30-8:55am

Systemic Factors associated with Diabetic Retinopathy

Emily Y. Chew, MD, National Eye Institute (NEI), National Institutes of Health (NIH)

In both type 1 and type 2 diabetes, the role of intensive glycemic control, with or without the combination of therapy for dyslipidemia and intensive blood-pressure control has been studied in randomized controlled clinical trials over the decades (Diabetes Control and Complications Trial [DCCT], Action to Control Cardiovascular Risk in Diabetes [ACCORD], and others). The importance of tight or intensive glycemic control has been proven to reduce the risk of progression of diabetic retinopathy in both types of diabetes and in persons with diabetes and with or without diabetic retinopathy at the time of initiation of tight glycemic control. Furthermore, the metabolic memory or the legacy effect of this tight glycemic control endured for over two decades. Tight glycemic control may also have beneficial effects on other diabetic complications. The treatment of hypertension has been proven in the United

Kingdom Prospective Diabetes Study (UKPDS) to be effective in reducing diabetic retinopathy progression and the development of diabetic macular edema. More recent studies have not demonstrated a beneficial effect partly because the standard arm is only 20 mmg Hg lower than the intensive treatment arm. However, lower blood pressure has been advocated by other studies such as SPRINT. Two studies of fenofibrate were designed to reduce elevated triglycerides to test the effect on cardivoascular risk as well as progression of diabetic retinopathy. The Fenofibrate Intervention & Event Lower in Diabetes (FIELD) study using 200 mg daily and the ACCORD study using 160 mg daily showed a beneficail effect in reducing progression of diaetic retinopathy, especially in persons with existing diabetic retinopathy. This treatment has not been adopted as standard medical practise because of the lack of efficacy for the systemic disease of cardivoascular events. Further discussion will be presented on this medical therapy. In summary, the control of glycemia, blood pressure and dyslipidemia has an important role in reducing the risk fo diabetic retinopathy progression.

8:55-9:20am

Update on the genetics of diabetic retinopathy

Lucia Sobrin, MPH, MD, Harvard Medical School, Mass Eye & Ear Infirmary

The underlying genetic risk factors for developing diabetic retinopathy 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 whole exome sequencing experiments. Ongoing investigations in the human genetics of diabetic retinopathy including pharmacogenetic studies will also be discussed.

9:20-9:45am

Molecular Mechanisms of Diabetic Retinopathy

George Liang King, MD, FARVO, Joslin Diabetes Center

The major risk factors of diabetic retinopathy are hyperglycemia, duration of diabetes, hypertension, and hyperlipidemia. However, it is extremely rare to develop the early pathologies of diabetic retinopathy without hyperglycemia. The pathogenesis of diabetic retinopathy is dependent on the stages of the disease and it is very clear that excessive production of VEGF (Vascular Endothelial Growth Factor) in the retina due to loss of capillaries with subsequent hypoxia is the major cause of proliferative diabetic retinopathy (PDR) and a significant of portion of people who have diabetic macular edema. The role of VEGF in causing PDR and macular edema has been substantiated by successfully using vitreous injection of anti-VEGF therapies. However, the mechanism for the cause of early changes of DR and a significant portion of macular edema are still unclear although multiple mechanisms such as oxidative stress, local inflammation, glycated products (AGE's) and protein kinase-C activation are still being considered. Recent studies have shifted the focus from risk factors to protective factors in the retina due to clinical reports that large number of people with type 1 diabetes with duration of 50 years or longer are protected from development of severe DR even in the presence of hyperglycemia for extreme long durations. The presence of these protective factors are now being investigated and identified as potential therapies for early DR and diabetic macular edema

9:45:9:55am: Discussion- 9:55-10:10am: Break

10:10-10:35am

Experimental models of diabetic retinopathy - Pros and cons

Sayon Roy, PhD, FARVO, Boston University School of Medicine

Much of the information regarding the pathogenesis of diabetic retinopathy (DR) has been derived through studies involving experimental animal models. The relevance of this approach using animal models hinges on the observation that results obtained through cell culture experiments require verification at the in vivo level. Pathological changes in DR have been studied using various animal models, genetic variants, chemical-induced variants, diet-induced variants and others. While these experimental models have certainly contributed to our understanding of DR pathology and subsequent drug development, some limitations in using these models exist. This presentation will focus on commonly used animal models and discuss their pros and cons in understanding cellular and molecular mechanisms underlying DR development.

10:35-11am

Interactions between microglia and Müller cells in diabetic retinopathy

Steven F Abcouwer, PhD, University of Michigan, Kellog Eye Center

The presentation will examine the roles of microglia and Müller cells in diabetic retinopathy, with a focus on the known interactions between these two cell types. Retinal microglia are innate immune cells that form horizontal arbors of dendrites in retinal plexiform layers and monitor neuron health and synaptic activity. Müller cells are specialized glial cells that radially span the retina and provide structural integrity, ion buffering, neurotransmitter recycle, trophic support and metabolic homeostasis to the neural retina. Both microglia and Müller cells are equipped to respond to environmental cues indicating infection, neural injury or neurodegeneration, and both can perform phagocytosis to remove dying cells and debris. In diabetic retinopathy these cells undergo reactive transformations known as astrogliosis and microgliosis, respectively. The seminar will discuss: how these cellular responses contribute to inflammation and vascular endothelial growth factor (VEGF) production, the factors triggering microgliosis and astrogliosis, and the roles of microglia and Müller cells in initiating and propagating these gliotic responses in the retina. Furthermore, the potential for therapeutic intervention by blocking or short-circuiting these responses will be discussed.

11-11:25am

Mitochondrial epigenetics

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

Mitochondria are considered to play central role in the development of diabetic retinopathy; their dysfunction initiates capillary cell apoptosis, a phenomenon which precedes the development of histopathology characteristic of diabetic retinopathy. Emerging evidence suggests that covalent modifications, caused by the environment of a cell, also alter gene expression without altering the base sequence of the DNA. These ‘epigenetic’ modifications can have pathogenic role(s) in chronic diseases such as cancer, corneal dystrophy and age-related macular degeneration. Diabetic environment produces many metabolic abnormalities in the retina, disturbing mitochondrial homeostasis. This presentation will discuss the role of epigenetic modifications in the mitochondrial homeostasis in the development of diabetic retinopathy.

11:25-11:50am

Down-regulation of PPARalpha expression in retinal inflammation in diabetic retinopathy

Jian-Xing (Jay) Ma, MD, PhD, University of Oklahoma Health Science Center

Diabetic retinopathy (DR) is a chronic, progressive and multi-factorial disorder with retinal microvascular dysfunction being the major component. Retinal inflammation plays a key pathogenic role in DR. Peroxisome Proliferator-Activated Receptor α (PPARα), a hormone-activated nuclear receptor, is known as an important modulator of lipid metabolism. Two large, longitudinal clinical studies reported independently that activation of PPARα by fenofibrate has robust therapeutic effects on DR in type 2 diabetic patients. PPARα is expressed at high levels in normal retinas, and retinal PPARα levels are down-regulated in diabetic human donors and diabetic animal models. We found that PPARα confers potent anti-inflammatory and anti-oxidant effects in the retina with DR. This presentation will summarize our recent studies on molecular mechanism underlying the anti-inflammatory activity of PPARα, which is responsible, at least in part, for the therapeutic effect of fenofibrate on DR. This presentation will also summarize our studies regarding the molecular mechanism for the diabetes-induced PPARα down-regulation in the retina.

11:50am-12pm: Discussion - 12-1pm: Lunch

1-1:25pm

Lipids and diabetic retinopathy

Julia V Busik, PhD, Michigan State University

Data from recent clinical trials demonstrate that in addition to the well-accepted role of hyperglycemia, dyslipidemia is an important, but often overlooked factor in the development of diabetic retinopathy (DR). Analysis of blood lipid profiles in DCCT samples established a tight association between the development of DR and dyslipidemia in type 1 diabetes, and several clinical trials using lipid-lowering medications, including FIELD and ACCORD Eye suggested a link between dyslipidemia and DR progression in type 2 diabetes. However, unlike macrovascular complications, where the direct correlation between pathology and circulating lipid levels is well established, the role of circulating lipids in microvascular complications is still controversial. Dyslipidemia is a complex disorder that involves both central, as well as organ-specific mechanisms. These include abnormal levels of lipids in the plasma that arise from a disproportion in metabolism, release and/or uptake by the adipose tissue as well as inefficient lipid removal from blood circulation. In addition to central regulation, most cells in the body have tissue-specific control of lipid uptake, remodeling, and elimination. This presentation will discuss the effects of diabetes on both central and retinal tissue-specific control of multiple lipid classes including fatty acids, triglycerides, cholesterol, and sphingolipids. Potential lipid-specific therapeutic approaches will be addressed.

1:25-1:50pm

The gut microbiome in diabetic retinopathy

Maria B Grant, MD, FARVO, University of Alabama - Birmingham

There are diverse and continually changing populations in the gut microbiota and its composition and function have important roles in health and disease. A link exist between the gut microbiome and retinal diseases such as diabetic retinopathy (DR). A gut-retina axis exists and modulation of the gut microbiome by diet, probiotics, or antibiotics may impact development of DR Type 2 diabetes (T2D) is associated with an altered gut microbiota and has been associated with increased inflammation, increased oxidative stress, and increased vascular permeability (Allin et al. 2015; Rowan and Taylor 2016). A connection between the gut microbiota and DR exists in the interaction of antihyperglycemic drugs and the microbiome. Metformin exerts a strong effect on the gut microbiome independent of the glycemic effect (Lee and Ko 2014; Forslund et al. 2015). Besides drugs, food and feeding patterns can influence the gut microbiome We asked if intermittent fasting (IF) can prevent DR. In db/db mice (a model of T2D), we examined the impact of long-term IF on diabetic retinopathy. Despite no change in glycated hemoglobin, db/db mice on the IF regimen displayed significantly longer survival and a reduction in diabetic retinopathy end points, including acellular capillaries and leukocyte infiltration. We hypothesized that the IF-mediated changes in the gut microbiota were responsible for the beneficial effects we observed. Microbiome analysis revealed increased levels of Firmicutes and decreased Bacteroidetes and Verrucomicrobia. Compared with db/db mice on ad libitum feeding, changes in the microbiome of the db/db mice on IF were associated with increases in gut mucin, goblet cell number, villi length, and reductions in plasma peptidoglycan. Consistent with the known modulatory effects of Firmicutes on bile acid (BA) metabolism, measurement of BAs demonstrated a significant increase of tauroursodeoxycholate (TUDCA), a neuroprotective BA, in db/db on IF but not in db/db on AL feeding. TGR5, the TUDCA receptor, was found in the retinal primary ganglion cells and retinal endothelial cells. Expression of TGR5 did not change with IF or diabetes. However, IF reduced retinal TNF-α mRNA, which is a downstream target of TGR5 activation. These findings support the concept that IF prevents diabetic retinopathy by restructuring the microbiota toward species producing TUDCA and subsequent retinal protection by TGR5 activation (Beli 2018).

1:50-2:15pm

Imaging in Diabetic Retinopathy

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

Imaging of the posterior pole plays a key role in management of diabetic retinopathy (DR). Retinal imaging in diabetes has been utilized for population screening, telemedicine, natural history studies and to assess response to therapy. Technological advances in the last decade have improved image acquisition, processing, reproducibility and comparability between sequential retinal examinations. Fundus photography and fluorescein angiography had previously been the main modalities to study diabetic retinopathy. Optical coherence tomography (OCT) imaging for commercial use was introduced in 2001 and provides a noninvasive, fast modality to evaluate diabetic macular edema (DME). New imaging techniques are continually being introduced while established ones are updated. OCT angiography (OCTA) is a relatively new, novel modality to image flow in the retinal and choroidal vasculature. OCT angiography provides more detailed information about the vascular changes in diabetic retinopathy, as it can segment the retinal circulation into individual vascular plexuses. It has recently been demonstrated that subtle abnormalities may be imaged using OCT of the retinal nerve fiber layer (RNFL) as well as with OCT angiography (OCTA) prior to developing visible diabetic

retinopathy. The current imaging techniques used to evaluate structural and functional changes in diabetic retinopathy will be reviewed.

2:15-2:40pm

Anti-VEGF therapy in diabetic retinopathy – Current status

Lloyd P. Aiello, MD, PhD, Joslin Diabetes Center

The treatment of diabetic retinopathy and subsequent visual acuity outcomes have been markedly improved by the advent of vascular endothelial growth factor (VEGF) inhibitors. Originally focused on the treatment of diabetic macular edema (DME), it is now well established that anti-VEGF therapy can have additional beneficial effects by reducing diabetic retinopathy severity and treating proliferative diabetic retinopathy (PDR). Furthermore, we now have direct comparisons regarding the efficacy of various VEGF- inhibitors in specific disease cohorts permitting informed choices of therapeutic options. Our understanding of the efficacy, timing, therapeutic response, treatment burden, pertinent clinical findings and side effects continue to expand with further analysis of prior trials and ongoing studies. In this presentation the current status of anti-VEGF therapy for DME, PDR and retinopathy severity will be discussed.

2:40-2:50pm: Discussion - 2:50-3:05pm: Break

3:05-3:30pm

Novel Pharmacotherapies in Development for Diabetic Retinopathy and Diabetic Macular Edema

Quan Dong Nguyen, MD, MSc, Stanford University

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 improvemnt 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 that are currently being investigated in clinical trials for patients with DME and/or DR.

3:30-3:55pm

How important are vascular stem cells for diabetic retinopathy

Alan W Stitt, PhD, FARVO, Queens University Belfast

This presentation will provide an overview of the pathogenesis of diabetic retinopathy and the various stages of the disease process where vascular stem cells may be involved. The talk will provide: 1. An outline of the various stem cell types, including their origins, molecular profile and pathophysiological

function in the context of the retinal vasculature.2. The relative importance of the vascular stem cell types in the context of a dysfunctional neurovascular unit, as occurs in diabetes.3. Mechanisms of how vascular stem cells become dysfunctional in diabetes.4. Do vascular stem cells offer innovative new therapeutic options for addressing different stages of diabetic retinopathy

Continuing Medical Education Agenda Ends

The presentations that follow are not included in the CME agenda for this course.

3:55-4:20pm

Emerging Concepts in Retinal Imaging and Drug Delivery

Ashwath Jayagopal, PhD F. Hoffmann-La Roche Ltd

We will discuss recent approaches for imaging and drug delivery for improving clinical management of DR. Key retinal imaging topics will include subcellular and molecular imaging approaches, and improvements in conventional imaging modalities. Retinal drug delivery technologies for achieving enhanced therapeutic durability and/or disease-specific therapy will also be discussed. We will also draw on approaches in other fields to identify promising technologies with potential ophthalmic applications.

4:20-4:25pm: Discussion - 4:25-4:30pm: Wrap up