June 28 (Friday) 9:00-10:50 Room 1 (Auditorium)

2nd International Workshop on Diabetic Retinopathy and Age-Related Macular Degeneration-DM

Chairs / Moderators: Susumu Ishida *(Japan)*
Shwu-Jiuan Sheu *(Taiwan)*
Quan Dong Nguyen *(USA)*

9:00-9:08 **Inflammatory mediators in the pathogenesis of diabetic macular edema**
Chang-Hao Yang *(Taiwan)*

9:08-9:16 **The Role of Interleukin-6 in Diabetic Macular Edema and Neovascular Age-Related Macular Degeneration**
Quan Dong Nguyen *(USA)*

9:16-9:24 **Pharmacogenetics of Angiopoietin2 for the Treatment of Diabetic Macular Edema**
Marten Brelen and Mary Ho *(Hong Kong)*

9:24-9:32 **Response to anti-VEGF drugs for diabetic macular edema**
Masahiko Shimura *(Japan)*

9:32-9:40 **Diabetic macular ischemia-the unmet need**
Shih-Jen Chen *(Taiwan)*

9:40-9:48 **Diabetic macular ischemia-new imaging insights and functional correlates**
Chui Ming Gemmy Cheung *(Singapore)*

9:48-9:56 **Before microaneurysm**
Seung-Young Yu *(South Korea)*

9:56-10:04 **Diabetic Retinopathy, The Indian Scenario**
Krishna Ramachandra Murthy *(India)*

10:04-10:12 **Applying Deep Learning for Diabetic Retinopathy Screening in Thailand**
Paisan Ruamviboonsuk *(Thailand)*

10:12-10:50 **Panel Discussion**

Diabetic retinopathy (DR) is recognized as an inflammatory disease, to which glucocorticoid drugs are applied when it is complicated by vision-threatening diabetic macular edema (DME). Vascular endothelial growth factor (VEGF), a molecule responsible for the pathogenesis of DR, induces not only angiogenesis but also inflammation as a causative factor for DME. Recent evidence suggests that various inflammatory cytokines other than VEGF are involved in the pathogenesis of DR, and development of new drugs targeting these cytokines are currently being explored. Moreover, recent advances in imaging technology have allowed more detailed analysis of vascular changes such as capillary dropouts. These ischemic changes on top of glucose toxicity cause the expression of VEGF and other inflammatory cytokines, leading to the complex molecular mechanism of DR. In this workshop, the world's leading experts will provide the latest information about the inflammatory pathogenesis of DR together with new treatment strategies beyond VEGF blockade.

Inflammatory mediators in the pathogenesis of diabetic macular edema

Chang-Hao Yang
Department of Ophthalmology, National Taiwan University Hospital, Taipei, Taiwan

Hyperglycemia could trigger inflammatory reaction and cellular apoptosis in retinal cells. Activation of transcription factor NF-κB plays an important role in these processes. NF-κB could induce the expression of various pro-inflammatory mediators which will participate in the pathogenesis of retinal cells damage.
The Silent information regulator T1 (SIRT1) is an NADC dependent class III histone deacetylases which could deacetylates histones and non-histone proteins, therefore modify many gene functions. SIRT1 could suppress NF-κB transcription by deacetylating the RelA/p65 subunit of NF-κB at Lys310 and inhibits NF-κB signaling. In diabetic retinopathy, hyperglycemia lowered the level of intracellular NAD+, and reduced the expression of SIRT1. Activation or overexpression of SIRT1 inhibits NF-κB transcription, thus prevent the DR progression.
Two clinical trials have shown that fenofibrate, a peroxisome proliferative-activated receptor type α (PPAR-α) agonist, reduces DR progression. PPAR-α is a regulator of inflammation by inducing the expression and activation of antioxidant enzymes. Recent studies have shown that there is a PPAR-α binding site in the promotor region of SIRT1 gene. Therefore, fenofibrate could protect retina from inflammatory reaction induced by high glucose in diabetes through the PPAR-α/ SIRT1/NF-κB signaling transduction pathway. Activation of PPAR-α may provide the pharmacologic therapies which could prevent DR progression and diabetic macular edema.

The Role of Interleukin-6 in Diabetic Macular Edema and Neovascular Age-Related Macular Degeneration

Quan Dong Nguyen
Spencer Center for Vision Research, Byers Eye Institute, Stanford University School of Medicine, Palo Alto, USA

Status of hypoxia and hyperglycemia can often lead to retinal damage, which leads to elevated level of interleukin-6 (IL-6) and pSTAT3, among others. Elevated levels of IL-6 have been detected in ocular fluid of patients with neovascular age-related macular degeneration (AMD), diabetic macular edema, and non-infectious uveitis. Baseline IL-6 levels appear unaffected by VEGF inhibition with VEGF antagonists such as ranibizumab. There appears to be a trend of lower best-corrected visual acuity (BCVA) gains in neovascular AMD and DME patients with higher baseline levels of IL-6.

Pharmacogenetics of Angiopoietin2 for the Treatment of Diabetic Macular Edema

Marten Brelen, Mary Ho
Department of Ophthalmology and Visual Sciences, The Chinese University of Hong Kong, Hong Kong, Hong Kong

Purpose: To determine the association of polymorphisms in the angiopoietin-TIE2 pathway with treatment responses of anti-vascular endothelial growth factor (VEGF) and/or AKB-9778 in diabetic macular edema (DME)
Participant: Patients were recruited from the TIME-2 clinical trial, involving 129 DME patients who were randomized to receive systemic subcutaneous AKB-9778 injections and/or intravitreal Ranibizumab to treat DME.
Methods: A Prospective cohort study. Forty-three single nucleotide polymorphisms (SNPs), including 30 TIE2 SNPs, 6 ANGPT2 SNPs, 5 PGF SNPs, CFH rs800292 and HTRA1 rs11200638 were genotyped. Multivariate analysis was used to determine the role of each SNP in treatment outcome measured at 12 weeks. Primary outcome included central subfield thickness (CST) and best corrected visual acuity (BCVA).
Results: 42 subjects were in the AKB-9778 group, 43 in the Ranibizumab group, and 44 in the combination group. A significant effect was identified between rs1014049 (P=0.01), rs666478 (P=0.002), rs2756901 (P=0.001), and rs625767 (P=0.039) in TIE2 and change in CST in all three groups. Patients with at least one effect allele [(rs549099 (P=0.047), rs2152065 (P=0.030), rs3737188 (P=0.008) and rs2756901 (P=0.001)] responded better than those without effect allele in the Ranibizumab monotherapy group. Patients with at least one effect allele [rs666478 (P=0.037) and rs625767 (P=0.008)] responded better in the combination group.
Conclusion: The presence of at least one effect allele was associated with an improvement of CST and BCVA, suggesting strong pharmacogenetic associations with the combination treatment. This finding could provide a more individualized treatment regimen based on patients' genotype in order to achieve optimal treatment responses in DME.

Response to anti-VEGF drugs for diabetic macular edema

Masahiko Shimura
Department of Ophthalmology, Tokyo Medical University Hachioji Medical Center, Tokyo, Japan

Although anti-vascular endothelial growth factor (VEGF) therapy improve visual acuity in patients with diabetic macular edema (DME), not all patients showed complete response to anti-VEGF therapy. In this study, required number of anti-VEGF injections at loading phase, and visual prognosis and total injection number during the clinical course of DME were assessed.
Eligible patients were treatment naive DME with central macular thickness (CMT) more than 400 μm, and loading monthly injections were continued until CMT less than 300 μm up to 6 injections. After that, additional injections were done with pro re nata (ranibizumab) or bimonthly (aflibercept) regimen. At the initial injection, aqueous humor in each case was collected.
According to our study results, a third of patients regressed edema after the 1st injection, in contrast, 10 % of them did not show enough response to anti-VEGF therapy after 6 loading injections. In the maintenance phase, PRN regimen showed slight decrease of VA, while bimonthly regimen showed slight increase of VA. Total required number of PRN regimen was 5.4 injections, which is significantly lower than bimonthly regimen of 7.1 injections.
Treatment regimen of anti-VEGF therapy for DME is still debate. Although response to anti-VEGF agents were case-dependent, continuous regularly injections at the maintenance phase may play a key role of better visual prognosis.

Diabetic macular ischemia-the unmet need

Shih-Jen Chen[1,2]

[1]Taipei Veterans General Hospital, Taipei, Taiwan, [2]National Yang-Ming University, School of Medicine, Taipei, Taiwan

Diabetic macular ischemia (DMI) is a clinically significant entity of diabetic retinopathy associated with chronic hypoxia of the retinal tissue. It can result in visual loss with or without diabetic macular edema. The damage to the retinal microvasculature can cause visual loss by affecting the inner retina as well as the outer retina due to the blunted autoregulation in diabetic vasculature that leave the photoreceptors vulnerable to decreased oxygen tension. Although recent OCT angiography studies showed that the ischemic parameters, such as size of FAZ, vascular density and vascular length at central 3x3mm are correlated with visual acuity in patients with diabetic retinopathy, their long-term change after anti-VEGF for concomitant diabetic macular edema were unknown. No defined treatment protocol for DMI had been devised at present. Increased oxygenation by hyperbaric oxygen therapy such as for diabetic foot ulcer had been tried to treat DMI with no consistent findings. Many aspects of DMI remained poorly studied and understood. A new image tool such as visible light OCT that could measure retinal oxygen metabolic rate non-invasively provided a potential to reveal the fundamental role of oxygen metabolism in DMI. This presentation will review the unmet need for DMI in the aspects of image studies, pathophysiology and therapy.

Diabetic macular ischemia-new imaging insights and functional correlates

Chui Ming Gemmy Cheung

Singapore National Eye Centre, Singapore, Singapore

Purpose: To evaluate the relationship between foveal avascular zone (FAZ) and perifoveal vessel density (VD) with best corrected visual acuity (BCVA) and retinal sensitivity, in persons with varying levels of diabetic retinopathy (DR).
Methods: FAZ areas and VD at the superficial and deep vascular plexus were evaluated based on OCTA in 40 diabetic patients prospectively recruited. Retinal sensitivity was measured using microperimetry and BCVA were correlated with OCTA measurements. Linear mixed models were used to determine the associations of DR severity with BCVA, retinal sensitivity, vessel density and FAZ areas.
Results: We included 80 eyes from 40 participants. Retinal sensitivity decreased as DR severity increased Vessel density decreased with increasing severity of DR. The FAZ areas were also larger at both the SVP and DVP for increasing severity of DR. Retinal sensitivity negatively correlated with superficial FAZ area. and positively correlated with vessel density.
Conclusion: DR level was associated with visual function and retinal microvasculature. There was correlation between retinal microvasculature and visual function as measured using microperimetry.

Before microaneurysm

Seung-Young Yu

Kyung Hee University Medical Center, Seoul, South Korea

Traditionally, the severity grading of DR has been based on structural changes within inner retinal microvasculature, and DR is considered to be a pathology of retinal vascular complications. However, retinal neurodegeneration has also been emphasized as an important and early component of the retinopathy. Diabetic retinal neurodegeneration (DRN) is described as a consequence of neural apoptosis, reactive gliosis, glutamate excitotoxicity, and impairment of the neurovascular coupling. We can assume that thinning of the mGCIPL is developed as a feature of systemic diabetic neuropathy in retina. Recently, OCTA revealed that early foveal microcirculatory alterations in diabetic eyes were related to mGCIPL thickness, regardless of the presence of DR. In addition, we recognized longitudinal change of OCTA metrics in diabetic eyes which resulted in significant impairment from 6-18 months. Progressive loss of mGCIPL thickness was strongly correlated with a decrease of retinal vessel density. Lastly, early microvascular damage was likely to develop in diabetic patients who showed rapid mGCIPL loss or low baseline mGCIPL thickness. Therefore, our results suggest that early detection of subclinical DR based on loss of mGCIPL thickness could provide timely recognition and management for patients at a greater risk of further microvascular impairment in DR.

Diabetic Retinopathy, The Indian Scenario

Krishna Ramachandra Murthy[1,2]

[1]Vittala International Institute of Ophthalmology, Bangalore, India, [2]Prabha Eye Clinic and Research Centre, Bangalore, India

Diabetes mellitus is the most common endocrine disorder and India has the highest number of diabetics living in any country. It is estimated that presently close to 60 million people are living with diabetes in India and this number is expected to rise to 100 million by 2030. Close to 70% of the population of India lives in the semi urban and rural areas. They are often unemployed and with limited access to basic health care facilities. The challenges in tackling diabetic retinopathy fall under
1) Screening for diabetic retinopathy,
2) Treating those identified with diabetic retinopathy
3) Ensuring compliance to treatment and follow up screening.

I will be describing our model of diabetic retinopathy screening and treatment in the South Indian District of Karnataka Screening for diabetic retinopathy is by using tele ophthalmology which helps reach a large number of people. Though tele-screening helps identify patients with diabetic retinopathy, they still need to travel long distances to avail treatment. Management of diabetic retinopathy entails repeated visits to eye clinics with multiple ophthalmic examinations and treatment sessions. This burden can be alleviated to a large extent if treatment is made available at the place of screening. An indigenously developed mobile Advanced Eye Treatment Unit is used for this purpose. Ensuring compliance to treatment and follow up is with the help of a robust electronic medical record which is capable of scheduling appointments and recalling missed appointments.

Applying Deep Learning for Diabetic Retinopathy Screening in Thailand

Paisan Ruamviboonsuk
Rajavithi Hospital, Bangkok, Thailand

Screening for diabetic retinopathy is a national project of Thai government to reduce the risk of blindness in patients with diabetes. Many models of the screening had been assessed in the past. These include store and forward telemedicine and training local non-ophthalmic personnel to be screeners.
With the advent of deep learning, a branch of artificial intelligence, for the screening of diabetic retinopathy which has been published in many studies recently showing that its accuracy was very high or even better than human trained graders, we tested the deep learning system in our Thai national screening program.
We included more than 20,000 retinal images of patients with diabetes in all health regions of Thailand and found the deep learning had a sensitivity of 97.5% whereas our trained graders had 75%, for specificity, deep learning had 96% whereas the graders had 98%. The panel of international retinal specialists graded the retinal images as standard in this study.