NEW FRONTIERS IN THE DIAGNOSIS & TREATMENT OF DIABETIC RETINOPATHY

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FINANCIAL DISCLOSURES

I am a paid consultant for the following companies:
- Konan Medical
- Optovue, Inc.

“These affiliations will not affect the content of this presentation.”

OBJECTIVES

- Diabetes and Demographic Trends
- What is Diabetic Retinopathy
- How Do We Detect Diabetic Retinopathy
- Assaulting Diabetes and Diabetic Retinopathy
- Prevention of Diabetes and Diabetic Retinopathy

Prevalence of Diabetes

2015

CDC Diabetes Statistics - 2017

- 30.3 million Americans
- 7.2 million undiagnosed
- 84.1 million with prediabetes or metabolic syndrome
- 1.4 million legally blind from diabetic retinopathy

Clinical Criteria Required To Diagnose Diabetes

- Fasting Blood Glucose Test
  - Blood glucose of 126 or above on 2 occasions
- Hemoglobin A1c Test
  - Average blood glucose measurement over preceding 3 months
  - 6.5 or above
- Oral Glucose Tolerance Test
  - Patient drinks a 75g loading dose of sugar water – wait 2 hours
  - Blood glucose above 200 is diagnostic for diabetes
- In most patients, the earliest sign of diabetes is profound insulin resistance

Institute for Alternative Futures 2014 Diabetes Model based on Boyle, Projection of the year 2050 burden of diabetes in the U.S. adult population.


Prevalence of Diabetes (Diagnosed and Undiagnosed)
“But none of my patients have these problems…”

How is Prediabetes Diagnosed?

Clinical Criteria Required To Prediabetes

- Fasting Blood Glucose Test
  - Blood glucose measurement of 100 or above
- Hemoglobin A1c Test
  - Average blood glucose measurement over preceding 3 months
  - 5.7 – 6.4 indicates prediabetes or hyperinsulinemia
- Oral Glucose Tolerance Test
  - Patient drinks a 75g loading dose of sugar water – wait 2 hours
  - Blood glucose above 140 is diagnostic for prediabetes

How is Metabolic Syndrome Diagnosed?

Need 3 of 5 Risk Factors for Metabolic Syndrome

- Large waistline
  - Above 40 inches for men
  - Above 55 inches for women
- High triglyceride level
- High blood pressure
- Low HDL cholesterol level
- High fasting blood sugar

Metabolic syndrome increases the risk of developing diabetes, heart disease and of having a stroke

Diabetes can produce any of the following ophthalmic manifestations

- Retinopathy
- Glaucoma
- Cataracts
- Cerebral nerve palsies
- Ocular surface disease
- Diabetic vitreopathy
- Diabetic retinopathy
- Deficits in visual function

Diabetic retinopathy is characterized by observable retinal vasculopathy

- Microaneurysms and other vascular leakage
- Hard exudates, macular edema
- Capillary occlusion, neovascularization

OCT-Angiography and multispectral imaging facilitates the early diagnosis of hyperinsulinemia

Recognizing the state of prediabetes has the potential to decrease the need or medical interventions later in life

Managing hyperinsulinemia also has the potential to improve both quality and quality of life and to decrease both mortality and morbidity

Hyperinsulinemia may precede hyperglycemia by up to 24 years

What is Diabetic Retinopathy?

Two distinct but inter-related disease processes:

- Microvascular disease of the retina that is based on the observation of vascular changes or the presence of abnormal vascular lesions
- Retinal neurodegeneration that is characterized by a loss/deterioration of neural elements of the retina
  - Ganglion cell bodies
  - Photoreceptors
  - Nerve fiber layer

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Microvascular disease visualized with color fundus photography
What is Diabetic Retinopathy?

- After prolonged hyperglycemia, the vascular endothelial cells are damaged.
- This leads to thickening of the capillary basement membrane thereby preventing pericytes from being in contact with endothelial cells.
- Pericytes are imbedded in the basement membrane of the blood vessels and help control the blood barriers.
- Drop out of the pericytes leads to breakdown of the blood-retinal barrier and the focal loss of pericytes leads to bulging of the capillaries and microaneurysm formation.
- Microaneurysms are not usually found in healthy eyes.

Microvascular disease visualized with multi-spectral imaging.

What About Subclinical Diabetic Retinopathy?

Subclinical diabetic retinopathy is the development of vascular abnormalities prior to the development of funduscopically-evident diabetic retinopathy.

- Up to 30% of diabetic macula edema is undetected by stereo funduscopy.
- Patients are 3x more likely to develop clinically-significant macula edema.
- Inner retinal thinning characterized by fadolt of the retinal nerve fiber layer and the ganglion cell complex — known as "Retinal Diabetic Neuropathy" — is detected with spectral-domain optical coherence tomography (OCT) retinal imaging.
- Patients have a 6-10x increased risk of stroke and heart attack.
- In one study of patients with diabetes and no clinical diabetic retinopathy, optical coherence tomography angiography (OCTA) vascular imaging reveals subclinical diabetic retinopathy in up to 34% of patients.
- 23% of patients had areas of capillary nonperfusion revealed on OCTA imaging.
- 36% of diabetic patients had foveal avascular zone remodeling revealed on OCTA imaging.

Microvascular disease visualized with multi-spectral imaging.

Early Treatment Diabetic Retinopathy Study

- Evidence-based population study conducted from 1985-1989.
- Investigated whether laser surgery or aspirin therapy was better at treating diabetic retinopathy.
- Study conclusion was that laser was the better treatment option.
- This study adapted the definitions and classifications that we use today.
- Detection of diabetic retinopathy is based on "findings observable upon Dilated Ophthalmoscopy".
- Why do we follow 28-year-old clinical guidelines in 2018?

Microvascular disease visualized with fluorescein angiography.

Retinal Blood Microcirculation

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2018

Vascular Abnormalities in Diabetes
- Remodeling of perifoveal capillaries
- Capillary dropout in the inner retina
- Enlargement of the foveal avascular zone
- Macular telangiectasis
- Microaneurysms
- Other retinal hemorrhages
- Hard exudates
- Neovascularization
- Macular edema

Superficial capillary plexus
Deep capillary plexus
Choroidal capillaries
Choroid

What How is Diabetic Retinopathy?

- Oxidative stress is a main causative factor in diabetic microangiopathy.
- Release of inflammatory proteins, leukostasis, and programmed destruction of endothelial cells and retinal ganglion cells and axons.
- Biochemical alteration results in a breakdown of the blood-retinal barrier and then hypoxia, vascular leakage and neovascularization characterize the retinal vasculopathy.
- Almost 6% of adult Americans with diabetes have sight-threatening retinopathy.
- Significantly Higher in African-American, Latino and Native American-ethnic groups.
- Macular edema is the most common cause of permanent vision loss.

Microvascular disease visualized with multi-spectral imaging.

What is Diabetic Retinopathy?

- As the disease gets worse over time, extra glucose is converted to sorbitol, which does not have the ability to diffuse out of cells.
- This creates an osmotic imbalance that leads to further weakening of the retinal capillary wall, leading them to burst and causing dot and blot hemorrhages.
- 30% of vascular lesions are found in the retinal periphery.
- Progression of diabetic retinopathy over time is the expected finding.
- Duration of diabetes
  - 11-13 years (33% of patients)
  - Over 15-years duration (42% of patients)
- Rate of diabetic retinopathy progression is significantly higher in African-American, Latino and Native American-ethnic groups.
- Neovascularization.
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Microvascular disease visualized with multi-spectral imaging.

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Microvascular disease visualized with multi-spectral imaging.
In diabetes, a structure-function relationship exists between neurodegeneration and vision loss. In many patients, retinal neurodegeneration leading to vision loss can be detected without visible retinal vasculopathy. Retinal neurodegeneration could be a biomarker for subsequent vascular damage to the retina. Retinal neurodegeneration could be a sign of more widespread damage to the neural system.

What About Subclinical Diabetic Retinopathy?

- Peripheral neuropathy
- Neuro psychological disturbances

How Do We Detect Diabetic Retinopathy in 2018?

RETINAL NEURODEGENERATION

- Optical coherence tomography
- Threshold visual field examination
- Frequency doubling technology
- 10-2 macula test protocol
- Color vision examination
- Electroretinography
- Contrast sensitivity
- Dark adaptometry
- Macular pigment optical density

RETINAL VASCULOPATHY

- Careful dilated fundus examination
- Peripapillary retina
- Optical coherence tomography
- Spectral domain
- Angiography
- Multi-spectral imaging
- Widefield retinal imaging
- Fluorescein angiography

RETINAL NEURODEGENERATION

Retinal Diabetic Neuropathy

- Conventional OCT imaging provides a more detailed assessment of retinal structure than ophtalmoscopy, fundus photography, or widefield retinal imaging.
- Diabetic retinal neuropathy manifests on OCT imaging as significant thinning of the retinal nerve fiber layer and ganglion cell and inner plexiform layers.

50-year-old black woman with a 25-year history of insulin-dependent diabetes and 20/25 visual acuity.

Frequency Doubling Technology Perimetry

- Progressively distinguishes diabetes and worsening diabetic retinopathy from age-matched normal subjects without diabetes.
- FDT perimetry is more sensitive than standard white-on-white automated threshold perimetry to accomplish this diagnostic function.

Ganglion Cell Complex Analysis

- Clinically significant ganglion cell complex focal loss volume predates observable retinal vasculopathy in 22% of patients with diabetes.
- An increase in myopia is accompanied by an increase in ganglion cell complex focal loss volume in patients with diabetes.
- Ganglion cell complex focal volume loss is accompanied by an increase in the cup-to-disc ratio in diabetic eyes.

A low spatial frequency sinusoidal grating that undergoes high temporal frequency counterphase flicker appears to have approximately twice as many light and dark bars than are physically present, a phenomenon known as frequency doubling.
Color Vision Testing
Dyschromatopsia of diabetes is a chromatic visual disturbance in association with retinal diabetic neurodegeneration that precedes clinical diabetic retinopathy in 40%-55% of patients. 
55%-65% of patients with clinical diabetic retinopathy have color vision defects.

Blue-yellow color vision deficiency is found in almost 90% of patients with diabetic retinopathy.


Selective loss of S-cone function predominates in diabetes.
- Short-wavelength cone paucity
- Heightened phototoxicity

Computer-assisted color vision testing determines the type of color vision defect and the severity of the dyschromatopsia.


Electroretinography
Light-adapted flicker ERG
- Elicits response from cone bipolar cells
- ERG waveform peak time has been shown to be a sensitive measurement in some patients with ischemic diseases such as diabetic retinopathy

Light-adapted flash ERG
- Early a-wave elicits response from cone system
- Positive b-wave indicative of cone bipolar cell function


Optical Coherence Tomography
Clinically significant macular edema may be present without visible vascular lesions and in the presence of 20/20 acuity.

Retinal thickening within 500 microns of the macular center
Hard exudates within 500 microns of the macular center with adjacent retinal thickening
One or more disc diameters of retinal thickening, part of which is within one disc diameter of the macular center.

Optical Coherence Tomography Angiography
A noninvasive examination technique that can visualize retinal blood microcirculation down to the capillary level.

The instrument creates angiograms by assessing the change in OCTA signal caused by flowing red blood cells.

In contrast to fluorescein angiography, OCTA data is three-dimensional and can be visualized in divided tissue layers.
Superficial Capillary Plexus

Deep Capillary Plexus

OCT angiogram is normal and includes vascular data from the retinal nerve fiber layer and ganglion cells.

Normal OCT angiogram appears as a uniform organization of mini vortexes.

OCT Angiography Abnormalities

- Abnormal presence of blood flow
  - Neovascularization
  - Anomalously small blood vessels
  - Microaneurysms
  - Focally-dilated vascular capillaries

- Absence of blood flow
  - Capillary dropout
    - This refers to areas devoid of flow signal that would normally be vascularized, characterized by a larger than normal gap between capillaries, sparse capillaries, or no capillaries
  - Retinal non-perfusion

OCT Angiography retinal imaging reveals subclinical diabetic retinopathy:

- Remodeling of the perifoveal retinal capillaries
- Enlargement of the foveal avascular zone
- Capillary dropout in the inner retinal layers
- Microaneurysms

Case Report -- “The Diabetes Patient”

- 30-year-old Black woman presents for her annual diabetes surveillance examination
- Previous eye examination with me 15-months earlier was unremarkable
- She has no visual complaints and no ocular symptoms
- Medical history is significant for a 5-year history of diabetes
- The disease is currently “well-controlled” with oral medication
- She is approximately 45 pounds overweight and admits to a poor diet and no regular exercise program
- Refractive error is slightly myopic and subjective refraction produces 20/20 visual acuity in each eye

Diabetic Eye Examination

The goals of the diagnostic evaluation in a patient with diabetes is to accomplish the following:

- Determine the presence or absence of diabetic retinopathy
- If diabetic retinopathy is present, classify the condition
  - Neurodegenerative
  - Vascular
- Identify and exclude any differential diagnoses
- Prescribe a treatment program
  - Diabetes surveillance examinations
  - Nutritional supplementation, diet and exercise
  - Referral back to medical doctor for more aggressive treatment
  - Referral to retinal specialist for local treatment

Multi-Spectral Imaging

Retinal Health Assessment (RHA):

- A digital ophthalmoscope that utilizes safe, light-emitting diodes of various colors to progressively examine the layers of the retina and choroid via spectral dissection
- RHA generated spectral image using yellow wavelength is tailored for metabolic monitoring of two regions:
  - Anterior retina
  - Mid-retina

Spectral images may highlight specific abnormal anatomic and metabolic signatures that cannot be visualized with ophthalmoscopy or color fundus photography.
Dilated Fundus Examination
“No observable vascular abnormalities”

Color fundus photography using white light to visualize the retina

Multi-Spectral Retinal Imaging
“No observable vascular abnormalities”

Spectral images using yellow light to visualize the retina

Spectral-Domain OCT Retinal Imaging
“No clinical diabetic retinopathy”

Spectral-Domain OCT Retinal Imaging
“No clinical diabetic retinopathy”

Spectral-Domain OCT Retinal Imaging
“Mild, non-specific structural abnormalities noted in both maculas”

GANGLION CELL COMPLEX ANALYSIS
No clinical evidence of retinal diabetic neurodegeneration with OCT imaging
- No perifoveal thinning
OCT-Angiography Retinal Imaging
“Subclinical diabetic retinopathy, Right eye”
Superficial capillary plexus
Deep capillary plexus

OCT-Angiography Retinal Imaging
“Subclinical diabetic retinopathy, Left eye”
Superficial capillary plexus
Deep capillary plexus

10-2 Threshold Visual Field Examination
“Mild, non-specific paracentral scotomas – both eyes”

Extended Color Vision Testing
“Tritan color vision deficiency in the right eye”
Anatomical location of the defect is receptor cells (cones and their ganglion cells) and/or the retinocortical neural pathways in the brain to the visual cortex.

ELECTRORETINOGRAPHY
RETeval measures visual function by using a full-field electroretinogram (ERG) testing protocol
ERG waveform implicit time has been shown to be a sensitive measurement in some patients with ischemic diseases such as diabetic retinopathy
The flicker electroretinogram is directly reduced in proportion to the degree of diabetic retinopathy

ELECTRORETINOGRAPHY
Confirmatory electroretinogram (ERG) was obtained with the RETeval device one week later.
Results are essentially identical to the patient’s initial ERG test
Implicit time changes over one week
- OD 34.5 milliseconds
- OS 34.1 milliseconds
(retest)
- OD 35.3 milliseconds
- OS 34.9 milliseconds
(retest)
TREATMENT GOALS AND OPTIONS

Delay the development of diabetic retinopathy
- Earlier diagnosis of diabetes and diabetic retinopathy
- Tighter metabolic control
- Diet, exercise, medicine, nutritional supplementation
- Routine dilated fundus examinations

Prevent sight-threatening diabetic retinopathy
- Local treatment options
  - Laser photocoagulation
  - Intravitreal injections of steroids
  - Intravitreal injections of anti-vascular endothelial growth factor agents (anti-VEGF)

RISK MANAGEMENT THROUGH EARLY DETECTION

- Consider screening for prediabetes, insulin resistance or subclinical diabetic retinopathy on asymptomatic adults of any age with a BMI ≥ 25kg/m² or ≥ 23 kg/m² in Asian-Americans who have one or more additional risk factors
- For all patients, screening for prediabetes, insulin resistance, or subclinical diabetic retinopathy should begin at age 45 years
- If the test results are normal, surveillance testing carried out at 3-year intervals is reasonable
- Get your eyes examined by a modern optometrist that follows evidence-based treatment guidelines

RISK MANAGEMENT THROUGH PREVENTION

- Exercise 30 minutes each day (soon after waking)
- Eat a predominately plant-based diet that minimizes added sugars
- Drink coffee or tea
- Sleep > 6 hours per night and < 9 hours
- Get your serum vitamin D > 40 ng/ml
- Do not smoke
- Live away from smog
- Breast feed
- Turn down the thermostat
- Reduce light at night
- Fast if you are obese

“DIVFUSS”
The Diabetes Visual Function Supplement Study

- Meaningful improvements in visual function can be obtained with nutritional supplements containing xanthophyll pigments, antioxidants, and selected botanical extracts
- Therapy is designed to disrupt established biological pathways in the pathogenesis of diabetic retinopathy
- Therapy may afford some patients protection against diminution in visual function associated with the onset and progression of diabetic retinopathy

DIABETES VISUAL FUNCTION SUPPORT STUDY

Results of DIVFuss show the test formula significantly improved contrast sensitivity, visual field, color vision, macular pigment optical density, symptoms of diabetic peripheral neuropathy and high-sensitivity C-reactive protein (hsCRP) compared with placebo, without affecting A1c levels.

DISCUSSION

- There are several ways to measure a person’s vision, and diabetes can produce abnormalities in all of them
- A dilated fundus examination is the current standard-of-care examination method for detecting diabetic retinopathy by optometrists and ophthalmologists
- Optical coherence tomography angiography (OCT-A) has proven that in many patients, changes to the foveal avascular zone and capillary nonperfusion can be imaged before abnormal vascular lesions can be detected during a dilated fundus examination
CONCLUSIONS

- Chronic metabolic alterations caused by diabetes can lead to neurodegeneration and vasculopathy
- In some patients with diabetes, neuroretinal degeneration occurs in addition to, and independent of, any visible vascular lesions
- Ignoring early signs of functional vision loss could lead to a permanent loss of vision
- To control test variability, each patient becomes their own control subject, so that change over time could become a measure of progressive damage

CONCLUSIONS

- Combining structural and functional testing improves the ability to diagnose subclinical diabetic retinopathy
- We should use measurements in one domain (structure or function) to support the interpretation of clinical measurements in the other domain
- We should remember that every patient with diabetes is different, every diagnostic test result has the potential to be different, and the relationship between structure and function measurements varies from patient-to-patient