COURSE 2
Diabetic Retinopathy and Imaging Technology: Confirmation of Diagnosis and Treatment Protocols

COPE Course 39686-PS

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Diabetic Retinopathy and Imaging Technology: Confirmation of Diagnosis and Treatment Protocols

Commercial Disclosure

- The content of this course was prepared independently by Drs. Gerstner and Ensor without any input from members of the ophthalmic industry.
- Drs. Gerstner and Ensor do not have financial interests in any companies, products, or services mentioned in this presentation.

Course Description

- Confirmation of diagnosis for diabetic eye disease
- Available technology
- Proper documentation utilizing technology
- Progression analysis with technology
- Local treatment protocols for diabetic eye disease

Course Goals

- Diabetes mellitus: metabolic disease review
- Systemic medications: pharmacology review
- Diabetic retinopathy definitions and review
- Landmark and recent studies
- Local treatment trends
- Imaging and technology
- Billing and coding guidelines
- Case presentations – diabetes and others

Overview of Diabetes Mellitus

- Diabetes is a group of metabolic disorders defined by elevated blood glucose resulting from insulin production defects, impaired insulin action, or both
- The 1997 International Expert Committee on Diabetes Mellitus changed the classification of diabetes, criteria for the diagnosis of diabetes, and control guidelines
- Revised guidelines were published in 2003

Overview of Diabetes Mellitus

- Type 1 (no longer considered IDDM or Type I)
  - Pancreatic beta cell destruction
  - Viral insult
  - 5% of all diagnosed cases
- Type 2 (no longer considered NIDDM or Type II)
  - Pancreatic beta cell inefficiency or insulin resistance
  - Age, obesity, and family history
  - 90% - 95% of all diagnosed cases
- Pre-diabetes
Overview of Diabetes Mellitus

- Gestational diabetes
  - 2% to 10% of all pregnancies
  - 5% to 10% will have diabetes immediately following pregnancy
  - 35% to 60% will develop diabetes in the next 10 – 20 years

- Other types
  - MODY 1 – 6
  - 1% to 5% of all diagnosed cases

Diagnostic Ranges of Diabetes

- Revised guidelines 2003

<table>
<thead>
<tr>
<th>Disease</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes Mellitus</td>
<td>1. FPG &gt; 126 mg/dL</td>
</tr>
<tr>
<td></td>
<td>2. Two hour PG &gt; 200 mg/dL with the OGTT after 75 g glucose load challenge</td>
</tr>
</tbody>
</table>

Diagnostic Ranges of Pre-Diabetes

<table>
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<th>Disease</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-diabetes (impaired glucose tolerance)</td>
<td>1. FPG level 100 – 125 mg/dL after over night fast</td>
</tr>
<tr>
<td></td>
<td>2. Two hour PG 140 – 199 mg/dL with OGTT after 75 g load challenge</td>
</tr>
</tbody>
</table>

How Many People Are Affected?

- Total: 25.8 million children and adults or 8.3% of the population
- Diagnosed: 18.8 million people
- Undiagnosed: 7.0 million people
- Pre-diabetes: 79 million people “Now 2013”
- New Cases: 1.9 million

The Diabetes “Belt”

- Total prevalence of DM, US 2013

Under 20 years of age: 215,000
1.9 million newly diagnosed
2 million aged 12-19 are pre-diabetic (1 in 6 are overweight)

Age 20 years or older: 25.6 million or 11.3% of all people in this age group
Age 65 or older: 15.9 million or 20.9% of all people in this age group
Men: 13.0 million or 11.8% of all men 20 years of age or older
Women: 12.6 million or 10.8% of all women 20 years of age or older
Diabetes Diagnosis

Diabetes – Lack of Activity

Pharmacological Treatment of Diabetes

- **Insulin**
  - Effects
    - Increases the storage of glucose (as glycogen) in the liver
    - Facilitates glucose transport into cells
      - Muscle cells
        - Stimulates glycogen synthesis and protein synthesis
      - Adipose tissue
        - Facilitates triglyceride storage

Insulin and its Analogs

- Human insulin is produced by recombinant DNA technology
  - Modification of amino acid sequence yields insulin with different properties
- Usually given by subcutaneous injection
  - Continuous pumps have become popular
- Excessive doses of insulin can lead to symptoms of hypoglycemia

Different Formulations

- **Rapid-acting Insulin**
  - Used to control postprandial glucose levels
- **Short-acting Insulin**
  - Used in emergencies or maintenance regimens
    - Requires injection at least 1 hr before meals
- **Intermediate-acting Insulin**
  - Often used in combination with above
- **Long-acting Insulin**
  - Control of basal insulin levels
Complications of Insulin Treatment

- Hypoglycemia
  - Result of excessive insulin effect
  - Treat with administration of glucose
    - NOT a diet coke!
- Formation of antibodies
  - Not as common with use of purified human insulin

Synthetic Amylin Analog

- Pramlintide
  - Used as adjunct to mealtime insulin
  - Delays gastric emptying
    - Decreases postprandial glucagon secretion
    - Improves satiety
  - Injected immediately prior to meals
  - Dose of rapid-acting insulin should be decreased by 50%

Oral Agents: Insulin Secretagogues

- Sulfonylureas
  - Examples: Glipizide, Glyburide
  - Mechanism of action
    - Promote insulin release from the B-cells
    - Reduce hepatic glucose production
    - Increase peripheral insulin sensitivity
  - Many drug-drug interactions
    - Check before you prescribe an oral medication

- Meglitinides
  - Repaglinide and Nateglinide
  - Mechanism of action
    - Bind to K channel and cause release of insulin
    - Much more rapid onset than sulfonylureas
  - Used postprandial
  - Commonly combined with metformin or glitazones

Oral Agents: Insulin Sensitizers

- Metformin
  - Reduce hepatic glucose production
    - Activate AMP-activated protein kinase (AMPK)
  - May also slow glucose absorption from GI tract
  - No risk of hypoglycemia
    - Decreases plasma insulin level
  - Also shown to reduce hyperlipidemia
    - Can cause loss of appetite
      - Patient loses weight
    - Drug of choice for newly diagnosed type II
Oral Agents: Insulin Sensitizers

- Thiazolidinediones (Glitazones)
  - Pioglitazone, Rosiglitazone
  - Exact mechanism of action not understood
    - Promotes glucose uptake and utilization in adipose tissue
    - No hypoglycemia
    - Involves gene regulation
    - Can prevent type 2 diabetes
    - Limited due to side effects of weight gain, heart failure, and unknown cancer risk

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Oral Agents: α-Glucosidase Inhibitors

- Acarbose and Miglitol
  - Taken at beginning of meals
  - Delay digestion of carbohydrates
  - Results in lower postprandial glucose levels
  - Do not stimulate insulin release OR increase insulin action in target tissues
  - Do not cause hypoglycemia when used alone
  - Side effects
    - Flatulence, diarrhea, and abdominal cramping
    - Patients with GI disease should avoid

Oral Agents: Dipeptidyl Peptidase-IV Inhibitors

- Linagliptin, Sitagliptin and Saxagliptin
  - Inhibit DPP-IV
  - DPP-IV responsible for inactivation of incretin hormones
  - Prolonging activity of incretin hormones results in increased insulin release in response to meals
  - Caution in renal dysfunction
  - Few side effects

Incretin Mimetics

- Exenatide and Liraglutide
  - Incretin hormones released after a meal
  - Responsible for 60 to 70% of postprandial insulin secretion
  - Act as agonists at GLP-1 receptors
  - Improve insulin secretion, slow gastric emptying, decrease food intake, and promote B-cell proliferation
  - Must be administered subcutaneously

Oral Agents: Sodium-Glucose Transport Inhibitor

- Canagliflozin
  - Approved in March 2013
  - Inhibitor of subtype 2 sodium-glucose transport system protein (SGLT2)
  - SGLT2 is responsible for most of the glucose reabsorption in the kidney
  - Blocking this protein causes blood glucose to be eliminated through urine
  - Some cardiovascular side effects being reported but final study results expected in 2015

- Empagliflozin
  - Same MOA but just recently received FDA approval

Dr. Gerstner & Dr. Ensor
Non-Proliferative Diabetic Retinopathy

- Mild NPDR
  - Microaneurysms
  - Occasional hemorrhages
  - Occasional exudate
  - CSME - maybe?

- Moderate NPDR
  - More of the same in 4 fields
  - Cotton wool spots
  - Venous beading or IRMA
  - CSME – maybe?

Non-Proliferative Diabetic Retinopathy

- Severe non-proliferative diabetic retinopathy
  - Worsening exudation and capillary occlusive changes
  - Extensive IRH, venous beading, IRMA, and macular edema
  - Venous “sausaging” and “loops”

4-2-1 RULE

Severe retinal hemorrhages in 4 quadrants
Venous beading in 2 quadrants
IRMA in 1 quadrant

50% risk of developing PDR within one year

Proliferative Diabetic Retinopathy

- Neovascularization of the disc (NVD)
  - Neovascularization that develops on the optic nerve or within one disc diameter of the optic nerve

- Neovascularization elsewhere (NVE)
  - Neovascularization anywhere in the fundus that is not NVD
  - Tends to develop at the junction between perfused and nonperfused retinal tissue

- Neovascularization of the iris (NIV)
  - Development of NVI is a threatening sign of NVG

- Vitreous hemorrhage
  - Bleeding from NVD or NVE

Loss of normal retinal perfusion and the development of neovascular proliferative tissue

Microaneurysm

Microaneurysm

Non-Proliferative Diabetic Retinopathy

- Severe non-proliferative diabetic retinopathy
  - Worsening exudation and capillary occlusive changes
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Loss of normal retinal perfusion and the development of neovascular proliferative tissue
Clinically Significant Macular Edema
- Retinal thickening within 500 µm of the center of the fovea

Clinically Significant Macular Edema
- Exudate within 500 µm of the center of the fovea with adjacent thickening

Clinically Significant Macular Edema
- Thickening of at least one disc diameter within one disc diameter of the center of the fovea

DCCT
- Diabetes Control and Complications Trial-retinopathy
  - Type 1 diabetes
    - Rare 5 years after initial diagnosis
    - 50% after 10 years of diagnosis
    - 95% after 15 years of diagnosis
    - Higher incidence of neovascularization (old data)
  - Type 2 diabetes
    - Retinopathy often at time of diagnosis
    - 48% after 5 years
    - 95% after 10 years
  - Intense control reduces risk by 76%

Diabetes – Control to Prevent Complications
- Intense blood glucose control (DCCT)
- Hemoglobin A1c (HbA1c) to monitor control
  - 6.0% or less for diabetics
  - 40% reduction of complications if HbA1c is reduced one percentage point
- Blood pressure control
  - 35% to 50% reduction in heart disease or CVA
  - Reduction of diastolic pressure from 90 mmHg to 80 mmHg decreases a major cardiovascular event by 50%
- Lipid control
  - Strict LDL control can reduce cardiovascular complications 20% - 50%

Clinical Studies and the Standard of Care
- Early Treatment Diabetic Retinopathy Study (ETDRS) facts on macular edema and laser photocoagulation:
  - Generally stabilizes visual acuity but often does not improve it
  - Consists of directly treating focal areas of leakage and placing a grid in areas of diffuse capillary leakage – guided by IVFA
  - Should be avoided in presence of significant loss of perifoveal capillaries
  - May take months to show resolution of thickening and resolution may take longer for exudates
Clinical Studies and the Standard of Care

- PRP facts:
  - Will not improve visual acuity
  - Macular edema may worsen (cystoid macular edema)
  - May cause loss of peripheral vision and night vision
  - Will not always cause NVD or NVE to regress
  - Indicated in NVI

Diabetic Retinopathy Study (DRS)
- NVD > 1/3 to 1/4 of disc area
- Any NVD with associated VH
- NVE with associated VH

High risk characteristics (HRC) treated with PRP have a 50% ↓ in severe vision loss

Diabetic Macular Edema

- Important ranibizumab studies for DME
  - READ
    - Ranibizumab 0.5 mg
    - Focal/grid laser photocoagulation
    - Ranibizumab 0.5 mg followed by laser photocoagulation
  - RESTORE
    - Ranibizumab 0.5 mg with sham laser
    - Focal/grid laser photocoagulation with sham injection
    - Ranibizumab 0.5 mg followed by laser photocoagulation
  - RESOLVE
    - Ranibizumab 0.3 mg vs. 0.5 mg vs. sham
  - RISE
    - Ranibizumab vs. sham
  - RIDE
    - Ranibizumab vs. sham

Diabetic Macular Edema Local Treatment Trends

- Lucentis or Avastin or Eylea?
- Combination focal laser for micro-A and edema away from micro-A
  - Needed for sustained effect if necessary
  - Laser at one week if marked edema
  - “Light”, or low intensity, and short duration laser burns, for grid laser to areas of edema
- NSAIDS and topical steroids?
- PPV

PDR Local Treatment Trends

- PRP
  - “Light” - less intense/energy and shorter duration laser burns
  - Larger number of smaller spots (moderate treatment) to reduce pain, field loss, dark adaptation issues, inflammation, CME, “RPE creep”, and eliminate retrobulbar injection of anesthesia
  - 30 day follow-up
  - Anti-VEGF if not responding to PRP
  - Combination of PRP and anti-VEGF
- Lucentis or Avastin or Eylea
  - Adjunct to PRP (both are permanent), and not FDA approved (yet)
  - Pre-vitrectomy to reduce bleeding
  - VH with neovascularization followed by PRP after hemorrhage clears
  - NVI or neovascular glaucoma

A Brief History of OCT

- Time domain (old) versus spectral domain (new)

CIRRUS HD – OCT 5000

- Macular cube 512 x 128
- Macular cube 200 x 200
- HD 5 - line raster
- Optic disc cube 200 x 200
- Anterior segment 5 - line raster
- Anterior segment cube 512 x 128
### CIRRUS HD – OCT 5000

**Macula Analysis**
- Macular cube 200 x 200 and 512 x 128
  - Macular thickness
  - 3D visualization
  - Ganglion cell OU analysis
  - Macular change analysis
  - Advanced RPE analysis
  - Advanced visualization

**HD 5 – Line Raster**
- 5 – line raster
  - High definition image

### Macula Analysis

### Field of View
- Single capture widefield image
  - 200 degrees

### The Retinal Image
- The image can be separated so that distinct retinal sub-structures can be visualized
  - Green and red lasers used to compose image
  - Green “channel”
    - Sensory retina through RPE
  - Red “channel”
    - RPE through choroid
  - Example
    - Choroidal nevus seen only on red channel
    - CHRPE seen on both channels

### The optomap Image
- The image can be separated so that distinct retinal sub-structures can be visualized
  - Green and red lasers used to compose image
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    - Sensory retina through RPE
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    - RPE through choroid
  - Example
    - Choroidal nevus seen only on red channel
    - CHRPE seen on both channels
Optos Advantages

- Wide field of view on single capture
- Ability to magnify image
- Rapid capture of image and immediately available for review
- FA capable
- Pediatric friendly
- Excellent for patient education

Patient Education

Optos Disadvantages

- Learning curve for capture
- Takes up a lot of space (old version)
- Encourages decrease in BIO skills (?)

Recent Version – Daytona

Image Examples

Atlas of Images
Billing and Coding

- Coding and Medicare allowable fee structure 2014
  - 92134: Retina = 42.79
  - 92250: Fundus Photography = 74.43

Billing and Coding – Pitfalls

- Vision insurance, medical insurance, or both?
- ICD-9 codes and "baseline" testing
- Photography and OCT
- Calendar year and OCT
- The eye is considered to be a single organ
- Clear documentation and interpretation
- Patient service report

Thank you!

- We are available for questions...