

Diabetes – The Epidemic

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The US Diabetes Epidemic

- 18 million Americans have diabetes
 - Most are Type 2
- 5 million Americans have diabetes and don't even know about it

Diabetic Retinopathy

- Most common late complication of diabetes
 - 100% with Type 1 diabetes
 - 60% with Type 2 diabetes
- Patients > 40 yrs old
 - 40.3% had diabetic retinopathy
 - 8.2% had vision threatening retinopathy

Incidence of Proliferative Retinopathy

Most common cause of blindness
Occurs approximately 10 years after onset of disease
As the population ages, the incidence of diabetic retinopathy will increase

Diabetic Retinopathy

- Incidence, progression and development of proliferative retinopathy
 - Greatest with Type 1 diabetes
 - Next greatest with Type 2 + insulin
 - Least likely with Type 2 and oral agents/diet

Retinal Damage

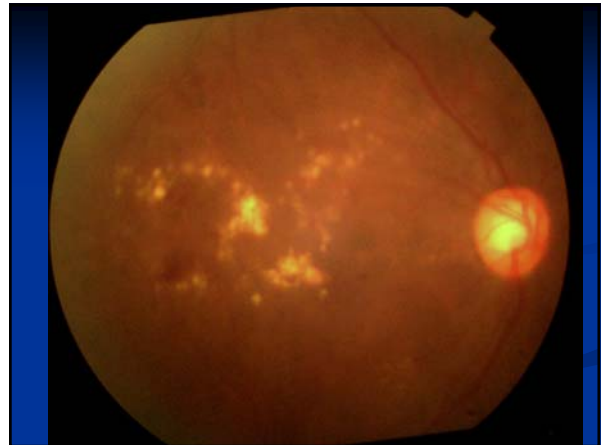
- Microvascular changes
 - Ischemia
 - Increase in vascular permeability
- Neuronal changes
 - Neurons
 - Glial cells
 - Microglia

Blindness in the US

- Diabetic retinopathy is leading cause of new blindness in Americans aged 20 – 74.
- Lower levels of vision loss can have significant effect on quality of life
- Diabetic macular edema (DME) is also a significant cause of reduced vision and blindness in patients with non-proliferative disease

DME

- Results in the increased vascular permeability
- Blood retinal barrier becomes compromised
 - Plasma leaks into surrounding retina
- DME may develop at any point during the progression of the retinopathy
- Most common in advanced stages



Laser Photocoagulation

- Two type of treatment
 - Panretinal
 - Focal
- Most widely used treatment for diabetic retinopathy
 - Limitations
 - Complications

New Attitude towards the Disease

- Prevent vision loss in the first place
 - Better glycemic control
 - Earlier detection*

New Research has New Focus

- Molecular biology
- Metabolic pathways
- Because of ever expanding population of diabetics, research and understanding is most critical

Costs of Diabetic Medical Care

- > 92 billion dollars in direct costs
- > 40 billion in indirect costs

Age when visual limitations are seen

- During those years when the individual is employed^Y
 - Consequences to the individuals family also

Classification of NPDR

- Mild NPDR - at least 1 ma (not severe hemorrhages or microaneurysms) less than 20 ma^Y
- Moderate NPDR (in between mild and severe)
- Severe NPDR – (4-2-1 rule)

4 – 2 – 1 Rule

- 4 fields of severe intraretinal heme
 - Or, 2 fields of definite venous beading (sausaging)
 - Or, at least 1 field of IRMA*
 - Third order of vascular branching (not usually seen in non-diabetic retinas)
- * IRMA = intraretinal microvascular abnormalities

Risk of Progressing from NPDR to PDR

- Mild NPDR has low risk
 - 5% PDR by 1 year
 - 15% by 5 years
- Moderate NPDR
 - 27% by 1 year
 - 33% by 5 years
- Severe NPDR
 - 52% by 1 year
 - 60% by 5 years

Very Severe NPDR

- Has 2 of the 3 features of the 4-2-1 rule
 - 75% PDR in 1 year

Value of F A

- Depends on availability of findings from second eye
 - If fellow eye has more DR, then chances are good that this eye will continue to deteriorate
 - If fellow eye has less DR, then chances are good that this eye will not continue to deteriorate
- Therefore, FA will not be indicated when fellow eye is visible to be seen to classify the patient as to risk of progression

Importance of Staging NPDR

- Mild NPDR: begin seeing every 12 months
- Moderate NPDR: begin every 6 months watching for progression
- Severe NPDR: see q. 3 months because they are at high level of risk for PDR
 - Laser photocoagulation might be indicated
 - If adult onset, then prp would be indicated
 - Focal photocoagulation would probably precede the PRP

Classification of Diabetic Retinopathy

- Level of Retinopathy
 - NPDR
 - Mild
 - Moderate
 - Severe
 - PDR
- Macular Edema
 - Present
 - Absent

Classification of PDR

- Four high risk features
 - Neovascularization
 - Neovascularization at the disc (NVD) or w/i 1 disc diameter
 - Severe NVE (>1/2 disc area) or severe NVD (1/3 disc area)
 - Pre-retinal (vitreous) hemorrhage
- *NVE = neovascularization elsewhere

PDR

- Non high risk if only 1 or 2 of the 4 high risk features
- High risk if 3 or 4 of the high risk features (requires PRP immediately)

Macular Edema

- Investigated independently of level of retinopathy
- At or near the fovea (clinically significant)
- Not near the fovea (not clinically significant)

Optometric Management Guidelines

- Mild NPDR c no macula edema
 - No photos except for baseline
 - No F A
 - No PRP
 - No focal laser
 - Follow in 12 mo.

Management Guidelines

- Mild NPDR c macular edema
 - Yes photos
 - Yes OCT

TYPICAL MANAGEMENT GUIDELINES

Level of PDR and Macular Edema	Color Photos	F A	PRP	Focal Laser	Follow-up
Non High-Risk PDR					
No macular edema	Y	N	O	N	2-4 months
Macular edema	Y	O	O	O	2-4 months
CSME	Y	Y	O	Y	2-4 months
High Risk PDR					
No macular edema	Y	N	Y	N	2-4 months
Macular edema	Y	O	Y	O	2-4 months
CSME	Y	Y	Y	Y	2-4months

New Mechanisms for Treating Macular Edema

VEGF Vascular Endothelial Growth Factor

VEGF₁₆₅ in Diabetic Retinopathy

- Retinal VEGF levels are elevated in animal studies
- Increased VEGF levels in vitreous of patients with PDR
- DR patients have higher levels of VEGF in aqueous

Protein Kinase C Beta in DR

- Activated by VEGF
- Mediates downstream effects of VEGF
 - Increased vascular permeability
 - Neovascularization

JAMA 2002; 288:2579-2588

Turning Science into Clinical Care

- Initial Exam
 - Fundus evaluation most important
 - May need photos* if difficult to get a good look (i.e. cataract, squeamish patient)
 - Goal is to detect when patient is at risk for losing vision (patient would be asymptomatic)
 - FA only when macular edema is present
 - Is it perfused or non-perfused edema (if perfused, from leaking vessels; if non-perfused, then source is from ischemia from thickening of tissue)

Treatment of patients with ischemic edema

- Not part of our understanding today. Perhaps a future drug will add to this

OCT with DR

- Greatly increased usage of OCT
- No data yet that addresses treatment outcomes
- Great teaching tool to demonstrate to patients
- Substitutes what we were trying to do before, and more accurately describes the anatomical function of the tissue

DME

- Who gets DME?
- Who loses vision from DME?
- Preventing DME
- Treating DME

Epidemiology

- 18 M people in US have DM
- Severe vision loss (SVL) mainly relates to proliferative diabetic retinopathy (PDR)
- Moderate vision loss (MVL) mainly relates to DME

Epidemiology con't

- T2 DM is 10x more common than T1 DM
- DME is more common than PDR in T2 DM
- DME is the leading cause of va loss

■ Schachet, AP et al, eds. Ryan's Retina Vol. II Medical Retina 3rd ed St. Louis CV Mosby Company 2000

Epidemiology of DR: WESDR

- T1 DM
 - 13% have DR @ 5 yrs disease duration
 - 90% at 10 – 15 yrs
- T2 DM
 - 40% of those taking insulin and 24% of those not taking insulin had retinopathy in 5 yrs
 - Increases to 84% and 53% respectively at 15 – 19 yrs disease duration

* WESDR: Wisconsin Epidemiology Study of Diabetic Retinopathy

Risk Factors for Retinopathy Progression

- Poor glycemic control
- Hypertension
- Elevated serum lipids
- Pregnancy
- Others

Which Patients Lose Vision?

- Which patients with NPDR lose vision from DME?
- Ocular risk factors
 - CSME
 - Thickening at or within 500 microns of the center
 - Hard exudates at or within 500 microns
 - Retinal thickening 1 disc area or larger, any part of which is within 1 disc diameter of the center of the macula
 - Identified from the ETDRS control group eyes

Definition of Thickening

- Clinical, “clinically significant macular edema” – not OCT edema
- Comparing our ability to detect macular edema upon visual examination to detection by OCT
- Needs to be about 300 microns of thickening to actually see it
- Normal thickness on OCT is 180 – 200
- The range between 200 – 300 is pre-clinical

Preventing DME

- Risk factor modification, chiefly glucose control
 - Diabetes Control and Complication Trial (DCCT) (Type 1)
 - U K Prospective (Type 2)
 - Diabetes Study (UKPDS)
- Experimental therapies
 - Protein kinase C (PKC) β inhibitors

Blood Sugar Control (Conventional vs. Intensive)

- By lowering the A1C from 9 achieved by conventional control to 7 achieved by intensive control, the amount of retinopathy was greatly reduced.
- About 5 years or more, the rate of CSME was significantly reduced on intensive control

Treating DME

- ETDRS: focal laser treatment
 - The gold standard of treatment
 - Main variable was loss of 3 lines of vision
 - 24% of control eyes reached this end point at 3 years vs. 12% of treated eyes (50% improvement)

Treating DME: Future Strategies

- Steroids
 - IVTA
 - Periocular steroids
 - Fluocinolone implants
 - Dexamethasome implants
- Anti VEGF agents
 - Pegaptanib (Macugen) injection
 - PKC β inhibitors

Clinical Trials

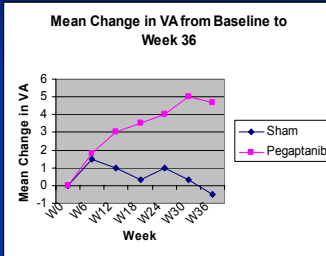
- 24 month Data: Fluocinolone implant
 - Mean change in va at 24 mo ($P=.003$)
 - No significant improvement
 - \$7,000 - \$8,000
- Dexamethasome Implant
 - 2 line improvement in 90 days
 - 3 line improvement in 180 days
 - Phase 3 trial underway
 - Clear dose response relationship between 350 μ g and 700 μ g doses

Clinical Trials

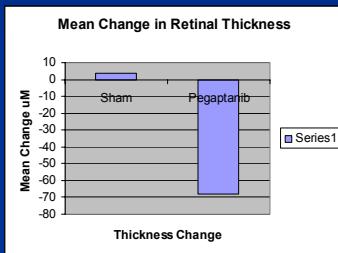
- Pegaptanib Sodium Injection
 - Phase 2 Study
 - 172 patients randomized
 - Median va at week 36 was 20/50 compared to 20/63 with the sham patients
 - 34% of the patient gained 3 lines compared to 10%

Pegaptanib, cont

- Mean central retinal thickness decreased by 68 μm vs an increase of 4 μm with sham
- Larger % of those receiving treatment had an absolute decrease of 100 μm (42%) than sham (16%)



Pegaptanib, cont



Pegaptanib, cont

- Photocoagulation was deemed necessary in only 25% of subjects vs. 48% with sham

Ruboxistaurin (Arxxant)

PKC - β Inhibitor

Arxxant

- Compared to placebo, 32 mg/day RBX was associated with delayed occurrence of MVL and SMVL
- This was most evident in patients with DME at baseline

DME: Summary and Conclusions

- Key risk factors
 - Duration of diabetes
 - Blood sugar control
 - Hypertension
- Modifiable risk factors
 - Glycemia
 - Hypertension

DME:

- Laser photocoagulation is the one proven standard treatment
- Intravitreal steroid therapy is promising and under study
- Anti-VEGF data looks favorable
- PKC- β inhibitor met a vision endpoint for patients with DME

Case Study

- Patient in their 60's
- DME

Case Study

- Color Photo didn't show much, even with marked thickening, so sometimes tricky to diagnose
- DME with diffuse accumulation of retinal fluid
- Small amount of retinal neovascularization
- Laser treatment will reduce the risk of vision loss by about 50% if no treatment
- Chance of vision gain is small (10% in EDTRS)

Case Study

- This patient had reduced vision because of increased thickening
- Focal laser treatment gives this patient a 1 out of 6 chance of not losing vision compared to 1 out of 3 if left untreated
- If OCT shows no improvement in thickness, might try anti_VEGF treatment
- Don't like steroids (injection or Retisert) because of glaucoma and cataract complications

OCT

- Anatomic correlate that might be improved surgically

General Medical Care of the Diabetic

Diabetes 2006

New Concepts

- Evidence is now overwhelming that good blood glucose control slows or prevents the progression of microvascular disease, including DR
- The tools are available to achieve better glycemic control, albeit only with dedicated patient self-care

New Concepts

- The tools are available to assess how the diabetic is doing, and these tools should be used
- The future of diabetes care will be better and better, easier on the patient

New Concepts

- The evidence exists that good control of glycemia minimizes microvascular complications
- The evidence suggests that even mildly impaired glucose intolerance, even pre-diabetes, increases the risk of CVD

Type 2 Diabetes

- Nutrition and Exercise



- Oral Agents



- Insulin

Nutrition and Exercise

- Still promoting hypocaloric, hypolipidemic diet
- Still seeking consistency of intake
- Still arguing about carb vs fat content

Nutrition and Exercise

- Glycemic Index: how high 100 gm of a given source of carbohydrates raises plasma glucose
 - White bread
 - Rarely practical for a diabetic
 - Fraught with confounders, such as what else was in the meal
 - E.g. high fat meals slow the absorption of carbohydrates

Nutrition and Exercise

- The more unstable a person's diabetes is, the more emphasis on carbohydrate awareness and carbohydrate counting
- Most important in Type 1
 - Juvenile onset
 - Insulin dependent

Nutrition and Diet

- The more overweight a person is, especially with Type 2 diabetes, the more emphasis should be put on weight reduction which is usually dietary fat reduction

Oral Agents

- 3 Major Classes
 - Sulfonylureas
 - Metformin
 - Thiazolidinedones (TZDs)

Oral Agents: Side Effects

- Sulfonylureas
 - Clinical hypoglycemia
- Metformin
 - GI side effects
- TZD's
 - Fluid retention
 - Weight gain

A New TZD

- Muraglitazar (Pargluva)
- Ppar α^* and γ (gamma)
 - Better lipid lowering effects*
 - Current TZDs negative on triglycerides and HDL
 - Equal glycemic effects as earlier TZDs
 - Same fluid retention and weight gain side effects

Insulin

- Human is universally used now
- Beef and pork insulin no longer used
- Insulin analogs often used
 - Fast acting insulin lispro, aspart
 - Ideal for pre-meal to handle that meal only
 - Long acting insulin gargine, detemir
 - Longer than NPH, ultra-lente insulins
- Widespread use of insulin pumps
 - Not a “demand” system, must be signaled

Inhaled Insulins

- Exubera
 - Short acting
 - Short duration
 - Before meals, not after and not hs
 - Contraindicated in smokers and people with pulmonary disease

Tools for assessing Diabetes (Glycemia)

- Self-monitoring of blood glucose
- Hemoglobin A1c
 - Average blood glucose over a number of months

Hemoglobin A1c

- Gold standard of glycemic control
- Done q 3 mo.
- Represents mean glycemia
 - <6% = normal
 - 6% - 7% = excellent, meeting standards
 - 7% - 9% = could be improved
 - >9% = poor control

Continuous Glucose Monitoring

- External
 - Short lived (15 hr – 3 days)
- Implanted
 - Subcutaneous (6 months)
- Much research, could be a reality in 5 years

The Cure of Diabetes

- Biological Approaches vs Mechanical Approaches

Biological Approaches

- Organ transplant
 - Kidney in end stage renal disease
 - Islet cell transplant
 - Embryonic stem cells
 - Adult stem cells

Mechanical Approaches

- External open-loop pumps
- Implantable open-loop pumps
- Continuous glucose sensing systems
- Implanted or external closed loop systems

Thank You From the Bottom of My
Pancreas