Essentials in Systemic Disease: Beyond Retinopathy: 13 Key Factors in Diabetes Wellness

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The Eye is an extension of the Brain
Neuroembryology

Beyond Retinopathy: 13 Key Factors in Diabetes Wellness

The Future
By 2050 - 100 million Americans will have diabetes

Epidemiology
7th leading cause of death in the US
> 25 million people with diabetes, costing $132 billion
75 million people have pre-diabetes

Leading Causes of Death in 2010
1. Heart disease: 597,689
2. Cancer: 574,743
3. Chronic lower respiratory diseases: 138,080
4. Stroke (cerebrovascular diseases): 129,476
5. Accidents (unintentional injuries): 120,859
6. Alzheimer's disease: 83,494
7. Diabetes: 69,071
8. Nephritis, nephrotic syndrome: 50,476
9. Influenza and Pneumonia: 50,097
10. Intentional self-harm (suicide): 38,364

The Prevalence of Diabetic Retinopathy
- Hispanic population tends to have the highest prevalence rates of Diabetic Retinopathy
- African Americans tend to have highest rates of vision threatening Diabetic Retinopathy
- No prominent difference between genders were seen in the prevalence of diabetic retinopathy
- The prevalence of diabetic retinopathy is in older age groups
Diagnosing diabetes – blood tests

- Fasting plasma glucose (PG) ≥ 126 mg/dL
- 2 hr PG during 75 g OGTT ≥ 200 mg/dL.
- Random PG ≥ 200 mg/dL PLUS symptoms of diabetes (polyuria, polydipsia, unexplained weight loss)
- A1C ≥ 6.5% (5.7% - 6.4% Pre-diabetes)

Diabetes is a disease of impaired insulin action

- Decreased insulin production
- Resistance to insulin action

Classification of Diabetes

- Type I diabetes
- Type II diabetes
- Gestational diabetes
- Secondary diabetes

Secondary Diabetes

- Pancreatic disease
  - chronic pancreatitis
  - tumor/resection
- Endocrine disorders
  - acromegaly
  - Cushing’s syndrome
  - pheochromocytoma/glucagonoma
- Drugs
  - thiazides, steroids, antipsychotics

Diabetic Retinopathy

- Hyperglycemia
- Platelet abnormalities
- RBC abnormalities
- Increased inflammation
- Autoregulation of blood vessels
- Histamine increase
- Increased whole blood viscosity
- Intraretinal growth factors
Diabetes is Inflammation

- Leukocytes, once inside the retinal tissue, then secrete a variety of inflammatory substances such as TNF and VEGF.
- These released mediators then increase vascular permeability and stimulate more mediators to enhance the inflammatory reaction.

Implicated Molecules

- Prostaglandins: Promotes vessel leakage
- Leukotrienes: Promotes vessel leakage
- Nitric Oxide: Promotes vessel leakage
- Protein Kinase C: Promotes vessel leakage
- Cytokines
  - VEGF: Promotes vessel leakage and bv growth
  - TNF: Promotes vessel leakage
  - IL-1: Promotes vessel leakage
  - IL-6: Promotes vessel leakage
  - IGF-1: Insulin-like growth factor 1
  - SDF-1: Stromal-cell derived factor 1

Diabetes and Ocular Manifestations

- Early Cataract
- Blurred vision
- Glaucoma
- Optic Neuropathies
- Retinopathy
- Ocular Ischemic Syndrome
- CRVO / BRVO

Sites of occlusion in Nl vs. Ischemic CRVO

Central Retinal Artery Occlusion

White opacification of retina; "cherry red spot"

Non-Proliferative Diabetic Retinopathy
Diabetes

Proliferative Diabetic Retinopathy

Hb A1C = 13 %
Some important systemic effects of diabetes and other conditions that affect Retinopathy and increase the risk of “Heart Attack”:

#1. HbA1C under 7% ADA, AACE <6.5%
Can be higher in patients with CVD, hypoglycemia, shorter life expectancy and children (7%-8%
ACCORD vs. ADVANCE studies

#2. Hypertensive patients with diabetes need a BP of 125/80 or better

#3. Cholesterol needs to be under control
LDL <100 mg/dl if no history of CVD, Pattern A vs. Pattern B
LDL <70 mg/dl if pre-existing history of CVD
HDLC >50 mg/dl in women and >40 mg/dl in men
Triglycerides < 150 mg/dl

#4. Sleep Apnea needs to be ruled out
CPAP - reduce nocturnal hypertension, increase oxygen, decrease FBS

#5. Anemia needs to be ruled out = hemaglobin needs to be above 11
Procrit (Epoetin alfa) needs to be considered if hemaglobin below 9. Starts early and has a negative impact on CV morbidity and mortality

>50% of persons with diabetes have concomitant hypertension and dyslipidemia

137,745 managed-care enrollees (Kaiser Permanente)

Obstructive Sleep Apnea

- Elevated morning BP by 20 -30 mmHg
- Elevated, resistant BP throughout the day
- Cong. Heart Failure, Nocturnal MI / CVA, Nephropathy
Glomerular Filtration Rate – test for renal function

According to the National Kidney Foundation, normal results range from 90 - 120 mL/min

Older people will have lower normal GFR levels, because GFR decreases with age.

Diabetes and high blood pressure are the two leading causes of kidney failure.

Chronic kidney disease (CKD) increases the risk of heart attacks and strokes.
Updated cholesterol guideline released November 13th, 2013 by the American Heart Association and American College of Cardiology aim to prevent more heart attacks and strokes than ever. How? By increasing the number of Americans who take a cholesterol-lowering statin.

The new guidelines recommend a statin for:

- Anyone who has cardiovascular disease, including angina (chest pain with exercise or stress), a previous heart attack or stroke, or other related conditions
- Anyone with a very high level of harmful LDL cholesterol (generally an LDL above greater than 190 milligrams per deciliter of blood [mg/dL])
- Anyone with diabetes between the ages of 40 and 75 years
- Anyone with a greater than 7.5% chance of having a heart attack or stroke or developing other form of cardiovascular disease in the next 10 years.

How is this different from the previous guidelines? They recommended specific cholesterol targets for treatment. For example, people with heart disease were urged to get their LDL cholesterol down to 70 mg/dL. The new guidelines essentially remove the targets and recommend basing treatment decisions on a person's heart risk profile.

In other words, anyone at high enough risk who stands to benefit from a statin should be taking one. It doesn’t matter so much what the actual cholesterol is as long as it’s below a certain level. What’s important is taking the right dose based on heart attack and stroke risk.

#6. Proteinuria (albuminuria) – Starlings Law (hydrostatic vs. osmotic)
30-299 mg = microalbuminuria
300 mg or more = albuminuria
ADA recommends yearly urinalysis followed by GFR
Start ACE inhibitors or ARB = renoprotective

#7. Stop smoking
Increases proteinuria, by wall damage, and vasoconstriction

#8. Vasculitis (R/O gum disease, leg ulcers, gastritis, urinary tract infections)
Daily aspirin decreases CVD in Type 1 and Type 2
ADA 81-325 mg/day
Not studied extensively for patients under the age of 30
CRP of 3.0 mg/L or higher can triple your risk of heart disease
CRP of 0.5 mg/L or less rarely experience heart attacks

The Vitamin D Epidemic

- Winter Influenza
- Winter Depression
- Cancer Belt: Northern Latitudes, Breast, Prostate, Uterine, Colon
- Loss of estrogen lowers vitamin D, Osteoporosis
- Winter Depression (Seasonal Affective Disorder)
- Low vitamin D
- Autoimmune Disease (Rheumatoid arthritis, Lupus)
- Organ Transplant Rejection
- Obesity (cardiovascular disease)
- Obesity (diabetes)
- Loss of muscle tone, heart failure, incontinence, falls

Diet provides only 10% of Vitamin D

THE VITAMIN D EPIDEMIC

### Did You Know...

Oral health affects overall health – left untreated, dental disease can cause medical conditions and even lead to death.

**Oral Health = Overall Health**
Get some sun
Not too much though

#10. Obesity - BMI (body mass index) less than 30 ....
better if less than 25
AACE recommends Bariatric surgery Type 2 patients with BMI > 35 kg/m².
Surgery is stressed if other conditions are present such as, pseudotumor cerebri, obstructive sleep apnea, hypertension, heart disease, polycystic ovarian syndrome.
The American Medical Association voted in 2013 to classify obesity as a disease.

The Pathology of Obesity

<table>
<thead>
<tr>
<th>System</th>
<th>Conditions</th>
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<tbody>
<tr>
<td>Skin</td>
<td>Yeast Infections, Gout, DJD</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Polycystic Ovarian Syndrome, low testosterone, high estrogen</td>
</tr>
<tr>
<td>Heart</td>
<td>Heart Attack, Stroke, CHF</td>
</tr>
<tr>
<td>Lung</td>
<td>Sleep Apnea</td>
</tr>
<tr>
<td>GI</td>
<td>Gallstones, GERD</td>
</tr>
<tr>
<td>Urinary</td>
<td>Incontinence</td>
</tr>
<tr>
<td>Gyno</td>
<td>Abnormal menses, Infertility</td>
</tr>
<tr>
<td>Neuro</td>
<td>Depression</td>
</tr>
<tr>
<td>Cancer</td>
<td>Breast cancer, colon, prostate, bladder and esophagus</td>
</tr>
<tr>
<td>Post-Op</td>
<td>Pulmonary embolism</td>
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</tbody>
</table>

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Genes and the relationship to obesity and inflammation

Dopamine Receptor DRD2 gene – linked to alcoholism, smoking, illicit drug use, gambling and overeating

Leptin Receptor LEP-R gene – linked to overeating and obesity

Mu-Opioid Receptor gene (OPRM1) – receptor for the most commonly used opioids such as morphine and heroin. May play a role in food addiction.
Visceral vs. Subcutaneous Fat

Visceral fat increases risk of diabetes, heart disease, dementia

20 oz bottle a day / year = 25 lb of fat per year

Beer belly = Soda belly

Sugars 101

Sucrose (table sugar) is broken down—in the body and (to some extent) in foods—to half fructose and half glucose. At that point it is essentially identical to high-fructose corn syrup.
Fructose (sucrose vs. high fructose corn syrup) consumption has increased in the last 30 years, coinciding with the obesity epidemic. Fructose is not glucose.

Hepatic fructose metabolism leads to all the manifestations of the metabolic syndrome:

- Hypertension – uric acid pathway (stopping nitric oxide)
- De novo lipid production, TG increase and FFA increase
- Inflammation
- Obesity
- CNS leptin (protein hormone) resistance promoting continuous consumption

Fructose is a hepatotoxin

Dr. Robert Lustig (UCSF)

Fructose is a carbohydrate

Fructose is metabolized as fat

- 30% ends up as fat
- A low fat diet is not really low fat
- Fructose/Sucrose doubles as fat

Fructose is a toxin

The FDA can’t and won’t regulate it
However ..........
Correlation does not mean causation

Risk Factors for the Progression of Diabetic Retinopathy

11. Insufficient Sleep -

- Increase in blood insulin and inflammation
- Sleep loss / decreased sleep quality = obesity and diabetes
- Short sleepers (< 7 hours) is increasing in AA and Hispanic
- Sleep deprivation = Decreased leptin and Increased ghrelin
- Decreased physical activity
- Increased cortisol release and increased insulin sensitivity
- Melatonin's role in diabetes?

29% of US adults sleep less than 7 hours per night
RF’s for the Progression of Diabetic Retinopathy

12. Chronic Stress –
- Leads to a change in gene expression and cellular aging
- Increase in cortisol, insulin, and inflammation
- Cortisol increases cytokine production and oxidative stress
- Telomere shortening – insulin resistance
- Prefrontal cortex overcome by limbic lobe and NA
- Stress and junk food = increase in visceral fat

#13. Vitamin B 12 deficiency in diabetics taking metformin

Vitamin B 12 deficiency in diabetics taking metformin
Medical Nutrition Therapy

ADA Guidelines = dietary caloric intake:

Low carbohydrate (50%)
   reduces post-prandial hyperglycemia

Low fat (30%)
   (eliminate trans fat, reduce saturated fat intake)

Low protein (20%)

Increase dietary fiber = DCCT decreases DR progression
10-30 gram / day, US = 12 gram
MNT lowers Hb A1C ~ 1

Dietary Fats

• Saturated fats – red meats (5 oz. or more), cheese, ice cream, butter, palm and coconut oils. Increases LDL. RDA = 10% of total calories or 20 grams/day

• Trans fatty acids – margarines, shelfed baked goods. Twinkies, pastries, donuts. Increase LDL, lower HDL, increase heart disease

• Unsaturated fatty acids – poly and mono Olive, peanut, sesame and canola oils, nuts, olives

• Cholesterol – < 200 mg a day (1 egg = 185 mg)
   7 eggs a week (yolk)

Milk comparison

Whole Milk
<table>
<thead>
<tr>
<th>Serving Size</th>
<th>8 fl oz (240mL)</th>
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<tbody>
<tr>
<td>Calories</td>
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<tr>
<td>% Daily Value</td>
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<tr>
<td>Fat</td>
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<tr>
<td>Saturated Fat</td>
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<tr>
<td>% Daily Value</td>
<td>25%</td>
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<tr>
<td>Cholesterol</td>
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<tr>
<td>Sodium</td>
<td>125mg</td>
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<tr>
<td>% Daily Value</td>
<td>5%</td>
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<tr>
<td>Total Carbohydrate</td>
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</tr>
<tr>
<td>Dietary Fiber</td>
<td>0g</td>
</tr>
<tr>
<td>Sugars</td>
<td>11g</td>
</tr>
<tr>
<td>Protein</td>
<td>8g</td>
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</table>

Skim Milk
<table>
<thead>
<tr>
<th>Serving Size</th>
<th>8 fl oz (240mL)</th>
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</thead>
<tbody>
<tr>
<td>Calories</td>
<td>80</td>
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<tr>
<td>% Daily Value</td>
<td>0%</td>
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<tr>
<td>Fat</td>
<td>0g</td>
</tr>
<tr>
<td>% Daily Value</td>
<td>0%</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>less than 5mg</td>
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<tr>
<td>Sodium</td>
<td>130mg</td>
</tr>
<tr>
<td>% Daily Value</td>
<td>8%</td>
</tr>
<tr>
<td>Total Carbohydrate</td>
<td>12g</td>
</tr>
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<td>Dietary Fiber</td>
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HIGH FRUCTOSE CORN SYRUP
Omega-3s (EPA and DHA)

- Decreases insulin resistance
- Decrease depression
- Prevent cardiac arrhythmias
- Increase Telomere length
- 1000 mg to 4000 mg / daily
- Ethyl ester vs. Triglyceride

EPA + DHA (Omega 3)
2 servings per week = 3.5 ounces cooked
1 gram per day if documented heart disease

Fatty fish:
• Salmon
• Herring
• Mackrel
• Trout
• Sardines

ALA = alpha linolenic acid
Kale
Spinach
Greens
Brussels sprouts
Can be converted to EPA and DHA in the body, however in very small amounts

Acetyl L Carnitine (ALCAR) 250 – 500 mg
- Is the acetylated ester of the amino acid L Carnitine
- Shown in clinical studies to support and improve mitochondrial functioning
- Used for heart and brain function, muscle movement

Coenzyme Q 10 (Ubiquinone) – 100 mg / daily
- Found in every cell of the body (mitochondria) – heart, liver, pancreas, kidney
- Functions in generating energy = ATP
- Salmon, Sardines, Tuna, Herring are sources

Is There a Strategy?

Taurine (400 mg)
- Amino Acids are the “building blocks” of protein
- Taurine supports glial function with the retina
- Taurine is found in high concentrations in the eye.
- It is the most abundant amino acid in the retina.
- Known to protect the body, and the eye from various toxins
- Has been shown to minimize diabetic retinopathy
Is There a Strategy?

Alpha Lipoic Acid (ALA)

- Naturally occurring compound synthesized by mitochondria
- ALA is a cofactor for enzymes producing ATP
- Dose ~ 200-400 mg oral supplementation are recommended for a therapeutic effect.
- Better absorbed on an empty stomach 1 hour before meals

Dietary Soluble and Insoluble Fiber

- Diabetes – stabilizes blood sugar, slows the absorption of carbohydrates, leads to less increase of blood sugar, less insulin release
- Cancer – high fruit and vegetable intake reduces risk (colorectal cancer)
- Stomach – reduces diverticular disease
- Heart health – lowers cholesterol
- Weight – promotes satiety
- Examples: Cereal 3 grams or more, oatmeal, Fruits, vegetables and whole grain products

Nutrition and weight loss: What works?

A moderate weight loss (5% of body weight) has been found to:

- Improve insulin action
- Decrease FBG concentrations
- Reduce the need for diabetic medication

10% of weight loss found a reduction in Hb A1C of 0.81%

3 types of diets for Type 2 diabetes

- Low Glycemic index diet
- Mediterranean diet
- Vegetarian diet

Because it burns calories? **NO WAY**!

- Exercise improves skeletal muscle’s insulin sensitivity
- Reduces stress and reduces cortisol release
- Improves hepatic insulin sensitivity (TCA cycle runs faster)

Tolerance
Dependance
**Added sugar:** Whether it’s white granulated sugar, brown sugar, high-fructose corn syrup, corn sugar, or honey, sugar contains almost no nutrients and is pure carbohydrate.

**Aspirin Use in Diabetes**

- Aspirin use in diabetic patients is *not associated* with an increased risk of hemorrhage or progression of retinopathy or macular edema !!!
- Aspirin use may actually slow the progression of diabetic retinopathy ???
- Aspirin Therapy (81-325 mg/day): ADA recommendations
  - Family History of coronary HD
  - Cigarette smoking
  - Hypertension
  - Obesity
  - Albuminuria
  - Elevated lipid levels
  - Age > 30 years
Stop Thrombus formation in the Diabetic

- Severe blockage of blood flow to the eye and orbit
- Carotid artery > 70% obstruction
- Poor collateral circulation between the external and internal carotid artery circulation
- Most cases are unilateral (80%)
- Pain in 40% of cases
- Dilated conjunctival vessels, mid peripheral retinal hemes, low IOP

Ocular Ischemic Syndrome

Proliferative diabetic retinopathy

Sleep Apnea = No “CPAP” use
Anemia = 8 Hb
Albuminuria = >100
BP 145/85
Smoker
Gum Disease
Vitamin D deficiency
HbA1C = 9 %
Hb A1C = 9.8%
Sleep Apnea = No “CPAP” use
Anemia = 8 Hb
Albuminuria = >300
BP 140/90
Smoker
Gum Disease
Vitamin D deficiency

Macrovascular Complications

- Coronary artery disease
  - Heart attacks
- Peripheral vascular disease
  - Limb Amputations
- Cerebral vascular disease
  - Strokes
- Renal vascular disease
  - Renal failure and dialysis

Conclusion:

- Protect the Eye = Protect the Heart

Take Home

- Diabetic Retinopathy is exacerbated by many concomitant conditions
- Control of the systemic aspects of the disease improves the systemic and ocular health
- Understand how Diabetic Retinopathy relates to the overall systemic health

The End!

- Thank you for your attendance
- My e-mail address: c pelino@salus.edu