NATUROPATHIC TX DPN

Copyright 2007, Emily Marie Splichal, esplichal@yahoo.com

Objectives

- What is *diabetic neuropathy* and what is the etiology?
- What are the *long-term complications* of diabetic neuropathy?
- What is the *current treatment* of diabetic neuropathy?
- What is R-*Lipoic Acid* and how is it different from current pharmaceutical treatments?
- What is the *future research* in alternative treatments for diabetic neuropathy?

Copyright 2007, Emily Marie Splichal, esplichal@yahoo.com

Hallmark of the "Diabetic State"

- Chronic Hyperglycemia
- Enhanced Superoxide and ROS Species
- AGE's and Lipid Peroxidation
- Decreased anti-oxidant defenses
- Increased oxidative stress markers – urine
- *Oxidative stress imbalance puts diabetic at risk for heart disease, microvascular complications, accelerated aging and cancer*

Copyright 2007, Emily Marie Splichal, esplichal@yahoo.com

Epidemiology

- ADA reports 20.8 million Americans (7% of population) has diabetes mellitus
- Approximately 500% of these will experience neuropathy
- DPN is #1 cause of non-traumatic amputations
  - 86,000+ amputations every year
  - 50% increase risk of a 2nd amputation in 5 years
    - After 2nd amputation 50% increase risk of death in 5 years
  - This incidence is dependent on the *duration of disease* and degree of *glycemic control*

Copyright 2007, Emily Marie Splichal, esplichal@yahoo.com

Diabetic Neuropathy

- Etiology & Diagnosis
- Types
- Long term effects of diabetic neuropathy
  - Muscle atrophy – Loss of coordination
  - Amputations
- Current treatment of diabetic neuropathy
  - Symptomatic
- R-Lipoic Acid
  - Benefits
  - Research
  - Adverse Effects
- Future Research
  - Acetyl-L-Carnitine, SOD, R-Dihydrolipoic Acid

Copyright 2007, Emily Marie Splichal, esplichal@yahoo.com

Etiology of Diabetic Neuropathy

- Complex, multi-factorial and not completely understood
- Chronic Hyperglycemia
- Oxidative Stress
  - Increases aldose-reductase activity
  - Reactive oxygen species (ROS)
  - Elevated oxidative stress markers
- Vascular Dysfunction
  - O2- and NO
  - Hypoxia and Ischemia

Copyright 2007, Emily Marie Splichal, esplichal@yahoo.com

Etiology – Chronic Hyperglycemia

- Enhanced formation of ROS from macrophages and mitochondrial end-products
- Associated increase in AGE's
  - Diet is a major source of exogenous AGE's
- Increased lipid peroxidation

Copyright 2007, Emily Marie Splichal, esplichal@yahoo.com

Etiology – Oxidative Stress

- Described by Baynes and Thorpe
- *Diabetes promotes a state hyperglycemia – glucose can react with ROS to form carbonyls – glyco-oxidation
- What is it? *Imbalance between oxidation products and anti-oxidant neutralizing defenses.*
- Chronic hyperglycemia & auto-oxidation
- A-Tocopherol
  - Main anti-oxidant in nerve membrane
  - Hyperglycemia reduces the binding of a-tocopherol to endothelial cells
  - A-tocopherol deficient diet causes reduction in autonomic nerves followed by sensory nerves
- Reduced Glutathione
- Inhibitory effect on NO-synthase resulting in decreased NO-dependent vasodilation

Copyright 2007, Emily Marie Splichal, esplichal@yahoo.com

Etiology – Microvascular Dysfunction

- *Endothelial dysfunction contributes significantly to diabetic vascular disease and is an important factor in the development of diabetic neuropathy*
- Superoxide anion formed in high quantities
  - Auto-oxidation of glucose
  - Superoxide directly reacts with smooth muscle causing contractions
  - Scavenges NO – further limiting vasodilation

Copyright 2007, Emily Marie Splichal, esplichal@yahoo.com

Etiology – Polyol Pathway

- Hyperglycemia causes an increases in aldose reductase activity
  - Enzyme which converts intracellular glucose to sorbitol
  - Accumulation of sorbitol causes tissue damage secondary to edema

Copyright 2007, Emily Marie Splichal, esplichal@yahoo.com

Types of Diabetic Neuropathy

- Autonomic
- Mononeuropathy
- Distal Peripheral Neuropathy
  - Motor Neuropathy
  - Sensory Neuropathy

Copyright 2007, Emily Marie Splichal, esplichal@yahoo.com

Long-term Complications of Diabetic Neuropathy

- Autonomic Neuropathy
  - Loss of sympathetic control
  - Neuropathic Edema
  - Monkenberg's Calcification
- Mononeuropathy
  - Cranial nerves – "Bell's Palsy"
  - Doesn't only occur in presence of PN or AN!
- Distal Peripheral Neuropathy
  - Loss of stability and coordinated gait
    - 15 x risk of falls
  - Leading cause non-traumatic amputations

Copyright 2007, Emily Marie Splichal, esplichal@yahoo.com

Diagnosis of Diabetic Peripheral Neuropathy

- History and Examination
- EMG/NCV
  - Large fiber
    - Proprioception, Position Sense, Unipedal stance
- Skin Biopsy
  - Small fiber
    - Temperature, Allodynia, Dec sweating

Copyright 2007, Emily Marie Splichal, esplichal@yahoo.com

Symptoms of DPN

- Large Fiber DPN
  - Weakness and muscle wasting
  - Decreased reflexes (decreased protective response)
  - Increase risk of charcot
  - Digital deformities
- Small Fiber DPN
  - Pain – sharp, stabbing, shooting
  - Thermal impairment

Copyright 2007, Emily Marie Splichal, esplichal@yahoo.com

Current Treatment for Diabetic Peripheral Neuropathy

- Pharmacotherapy vs. Alternative Treatments.
- Are we treating symptoms or the cause???
- Are we looking at the etiology of DPN?

Copyright 2007, Emily Marie Splichal, esplichal@yahoo.com

Pharmacotherapy

- Anti-Convulsants
  - Gabapentin (Neurontin)
    - Acts on Ca channels
    - Well tolerated
  - Pregabalin (Lyrica)
    - Requires lower doses than Gabapentin
    - Linear dose-therapeutic effect and little variability
    - No known drug-drug interactions
- SNRI's – Not SSRI's!
  - Duloxetine
- TCA's
  - Amytriptyline
    - Side Effects – dry mouth, blurred vision

Copyright 2007, Emily Marie Splichal, esplichal@yahoo.com

Alternative Therapy

- Physical Therapy
  - Anodyne – Infrared light
    - Increases neural blood flow
- Aldose Reductase-Inhibitors
- ACE-I
- Antioxidants
  - Vitamin E
  - *R- Lipoic Acid and R-Dihydrolipoic Acid*
  - Superoxide Dismutase
- Acetyl-L-Carnitine
- Benfotiamine

Copyright 2007, Emily Marie Splichal, esplichal@yahoo.com

R-Lipoic Acid

- "Super" Anti-oxidant
  - Regenerates Vitamin C and E
- Can be absorbed from the diet and cross BBB
- Stimulates GLUT4 receptors in skeletal muscle
- Low toxicity! Few adverse effects
- Research shown to increase endoneural blood flow, NO-dependent vasodilation, increase NCV
- In Vivo converted to *dihydrolipoate* (reduced form) acting conjointly with *a-tocopherol* as metal chelator
  - Binds superoxide and prevents lipid peroxidation
  - Requires NADPH – reduced in diabetes due to influx of glucose in aldose reductase pathway
    - Could you give Aldose Reductase-I with ALA??

Copyright 2007, Emily Marie Splichal, esplichal@yahoo.com

R-LA and DPN

- Best way to administer ALA?
  - IV vs po
  - What is the best dose of ALA?
    - 600mg or 1800mg
- What duration is best to see results?
  - Weeks, months, years?

Copyright 2007, Emily Marie Splichal, esplichal@yahoo.com

R-LA iv

- 3 week randomized controlled trial - *Intravenous*
- Measured Total Symptoms Score (TSS)
  - Burning, pain, numbness, prickling
- Two groups
  - 14 treatments 600mg IV vs. Placebo
- Results
  - Significant improvement in positive pain symptoms and negative sensory symptoms
  - Improve pathophysiology of nerves?

Ametov, A. *The Sensory Symptoms of Diabetic Polyneuropathy are Improved with Alpha Lipoic Acid*. Diabetes Care. 2003, 26(3): 770-774.

Copyright 2007, Emily Marie Splichal, esplichal@yahoo.com

R-LA po

- 3 week randomized controlled trial – *Per Oral*
- Measured Total Symptoms Score (TSS)
  - Burning, pain, numbness, prickling
- Two groups
  - 3 weeks 600mg po tid vs. Placebo
  - Pharmacokinetic studies have shown that 1800mg po ALA produces blood levels equal to 600mg IV ALA
- Results
  - Decrease of 47% in TSS in feet
  - Decrease in pain by 60% in ALA group

Ruhnaut, K. *Effects of 3-week Oral Treatment with the Antioxidant Thioctic Acid in Symptomatic Diabetic Polyneuroapthy*. Diabetic Medicine. 1999, 16: 1040-1043.

Copyright 2007, Emily Marie Splichal, esplichal@yahoo.com

Acetyl-L-Carnitine

- ALC is a key indicator of mitochonrial function
  - Shuttles fatty acids into the mitochondria for B-oxidation
  - Also plays role in electron transport chain
  - Supplementation of ALC in rats resulted in increased mitochondrial fx to a level of younger rat

Copyright 2007, Emily Marie Splichal, esplichal@yahoo.com

Acetyl-L-Carnitine and DPN

- Clinical studies suggest a ALC deficiency in diabetics with PN
  - Study by Vaughan looked at 24 Type 2 diabetics with DPN vs. 15 Type 2 diabetics without DPN and found a significantly lower serum carnitine levels in all DPN subjects
- Supplementation with ALC has shown to correct perturbations of neural Na/K ATPase, myoinositol, nitric oxide, prostaglandins and lipid peroxidation

Copyright 2007, Emily Marie Splichal, esplichal@yahoo.com

ALC and DPN

- What is the best dose of ALC?
  - 500mg vs. 1000mg t.i.d.
- What is the best way to administer ALC?
  - Im vs. po
- What is the duration till results?
  - 26 weeks vs. 52 weeks?
  - Length of diabetes dx.
  - Type 1 vs. Type 2 diabetes

Copyright 2007, Emily Marie Splichal, esplichal@yahoo.com

ALC 500mg vs. 1000mg/t.i.d.

- Two multi-center, double-blind, placebo controlled randomized 52 week prospective study (*Sima et al. 2005*)
- Efficacy end points
  - Sural n. morphometry, ncv, vbt thresholds, clinical symptoms score and VAS scale for pain
- Results
  - *500mg and 1000mg both resulted in significant increase in nerve fibers and regeneration clusters*
  - No significant changes in ncv for either group
  - Significant improvement vbt threshold in fingers for 500mg group and in both fingers and toes in 1000mg group
  - Clinical symptom score/VAS scale for pain

Copyright 2007, Emily Marie Splichal, esplichal@yahoo.com

ALC im and po

- Multicenter, double-blind, placebo controlled randomized 52 week prospective study (*de Grandis et al. 2002*)
- Efficacy end points
  - Sural n. sensory/motor ncv and VAS scale for pain
- Two groups
  - 1000mg im bid x 10 days followed by 2000mg bid/po x 355 day (n=167)

    vs. Placebo (n=166)
- Results
  - Placebo group had a decrease in sural n. mncv vs. an increase in all mncv and sncv treated with ALC
  - Decrease in pain on VAS scale was significantly greater in ALC vs. placebo group
  - Among pts with only sensory symptoms 8% in placebo group developed motor symptoms vs. 0% in the ALC treated group

Copyright 2007, Emily Marie Splichal, esplichal@yahoo.com

Benfotiamine and DPN

- Fat-soluble form of Vit B1 (thiamine)
- Has been used for decades in Europe as Rx
- Ameliorates the progression of diabetic nerve damage and relieves painful symptoms of DPN
- Benfotiamine acts by blocking biochemical pathways by which high blood sugar damages cells throughout the body

Copyright 2007, Emily Marie Splichal, esplichal@yahoo.com

Plasma glucose vs. Intracellular glucose

- Most diabetic medications and insulin work to control elevated *plasma* glucose levels
- Only benfotiamine lowers *intracellular* glucose and alters body's response to toxic breakdown products of excess sugar
- Benfotiamine stimulates the production of *transketolase*
  - Enzyme that efficiently converts potentially toxic glucose breakdown products into harmless compounds that can be safely eliminated by the body

Copyright 2007, Emily Marie Splichal, esplichal@yahoo.com

Benfotiamine and Endothelial Dysfunction

Copyright 2007, Emily Marie Splichal, esplichal@yahoo.com

Pathways inhibited by benfotiamine

- Inhibits 3 major pathways that lead to the formation of toxic substances such as AGE's
  - AGE's promote vascular damage, scar tissue and inflammation
  - Safe and well-tolerated

Copyright 2007, Emily Marie Splichal, esplichal@yahoo.com

Benfotiamine and DPN

- 3 week randomized controlled trial – 100mg qid
- Measured neuropathy symptoms and Vbt sensation scores
  - Burning, pain, numbness, prickling
- Two groups
  - 400mg po vs. Placebo
- Results
  - Significant improvement in positive pain symptoms

Haupt. E. *Benfotiamine in the treatment of diabetic polyneuropathy: a three week randomized, controlled pilot study*. Int J Clin Pharmacol Ther 2005, 43: 71- 77.

Copyright 2007, Emily Marie Splichal, esplichal@yahoo.com

Benfotiamine + B12

Copyright 2007, Emily Marie Splichal, esplichal@yahoo.com

Future Research…

- R-Dihydrolipoic Acid vs. R-Lipoic Acid
- Superoxide Dismutase
- Glutathione iv

Copyright 2007, Emily Marie Splichal, esplichal@yahoo.com

Why Consider Neutriceutical Therapy for DPN

- Must consider *etiology* of DPN
- Research shows promising effect on NCV
  - Why?
    - Reduced ALA binds Superoxide, preventing it from binding NO and inhibiting vasodilation
    - Remember vascular dysfunction association with DPN
- Remember importance of glycemic control in prevention and management of DPN
  - *ALA stimulation of GLUT4 receptors*
  - Exercise plays important role in insulin sensitivity, glucose control and DPN

Copyright 2007, Emily Marie Splichal, esplichal@yahoo.com

Thank you!!

Special Thanks to the New York Podiatric Medical Association

Copyright 2007, Emily Marie Splichal, esplichal@yahoo.com