Exercise for the Prevention and Management of Diabetic Peripheral Neuropathy

PRESENTED BY: EMILY SPLICHAL, BS, CPT
DPM/MPH CLASS OF 2008
NEW YORK COLLEGE OF PODIATRIC MEDICINE

Objectives

- Discuss the prevalence of DPN and the need for a prevention program
- Discuss the importance of understanding the etiology of DPN and implications of DPN on fx
- Discuss the benefits of exercise – especially resistance training – for diabetic
- Describe how balance training can reduce falls in pts already experiencing DPN
- Recognize the need for podiatrists and public health professionals to understand the benefits of exercise for their diabetic pts.

Hallmark's of 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*

Diabetic Neuropathy

- Etiology & Diagnosis
- Types
- Long term effects of diabetic neuropathy
  - Muscle atrophy – Loss of coordination
  - Amputations
- Current treatment of diabetic neuropathy
  - Symptomatic
  - Pharmaceutical vs. Naturopathic
- Exercise and the Diabetic
  - Resistance Training
  - Balance Training

Etiology of Diabetic Neuropathy

- Chronic hyperglycemia
- Oxidative stress
  - Increases aldose-reductase activity
  - Reactive oxygen species (ROS)
  - Elevated oxidative stress markers
- Vascular Dysfunction
  - O2- and NO
  - Hypoxia and Ischemia

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

Etiology – Oxidative Stress

- 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

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

Diagnosis 0f Diabetic Peripheral Neuropathy

- History and Examination
- EMG/NCV
  - Large fiber – Proprioception, Position Sense
- Skin Biopsy
  - Small fiber – Temperature

Types of Diabetic Neuropathy

- Autonomic
- Mononeuropathy
- Distal Peripheral Neuropathy
  - Motor Neuropathy (Large fiber)
  - Sensory Neuropathy (Small fiber)

Long-term Complications of Neuropathy

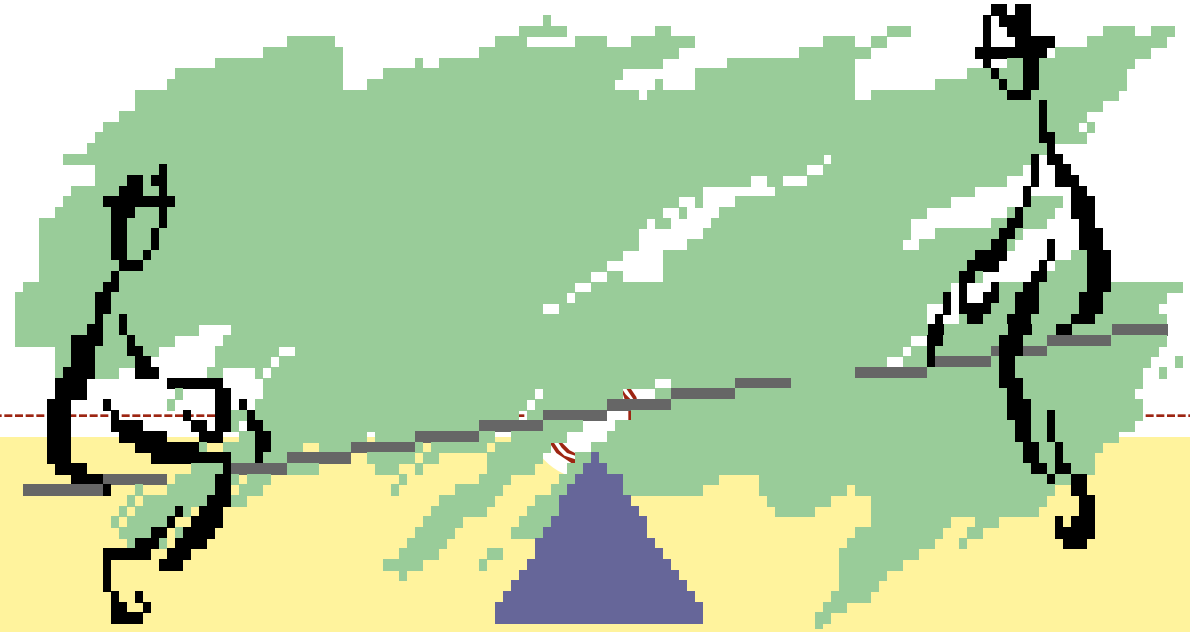
- Autonomic Neuropathy
  - Loss of sympathetic control
  - Neuropathic Edema
  - Monkenberg's Calcification
- Mononeuropathy
  - Cranial nerves – "Bell's Palsy"
  - Doesn't only occur in presence of PN or AN!
- Distal Peripheral Neuropathy
  - Loss of stability and coordinated gait
    - 15 x risk of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

Prevention and Management of DPN

- *Best way to control the onset of DPN is through tight glycemic control
- *Best way to control blood sugar is through exercise
- *Together diet and exercise can control DPN – which means decreased risk of ulcerations which leads to fewer amputations which saves billions of $$ each year

Aerobic vs. Resistance Training??

- Which is correct?
- Which gives the client the better glycemic control??
- Cardio burns the most calories right?? But resistance training builds muscle to increase metabolic rate??
- Remember we are trying to correct **hyperglycemia** and complications...



INTERESTINGLY...THE BENEFITS OF *RESISTANCE TRAINING* GREATLY OUTWAY THE BENEFITS OF *AEROBIC TRAINING*

Benefits of Exercise

- Cardio
  - VO2 Max
  - VO2 Kinetics
  - Slight decrease bp
- Resistance Training
  - Increase insulin sensitivity
  - Improve endothelial function
  - Improve lipid profile
  - Increase bone density

Types of Resistance Training

- **High Intensity**
  - **75-85% 1 RPM, 6-8 reps**
- Moderate Intensity
  - 50-60% 1 RPM, 8-12 reps
- Low Intensity
- **Circuit Training**
  - **Maintain hr**

The "Why" and "How" of Resistance Training

- Primary manifestation of diabetes is in the **skeletal muscle** (receptors)
  - Decrease glucose transport
  - Decreased GLUT4 expression
  - Decreased glycogen synthase activity
- What does this all mean??
- Can we target insulin action to GLUT4 through exercise? And thus help establish normoglycemia
  - Can normoglycemia established through exercise decrease the number of free radicals and sorbitol – and therefore decrease amount of damage to peripheral nerves/myelin??

Insulin-Receptor Pathway

- Insulin secreted by pancreatic B cells in response to increased blood sugar
- **Anabolic** (building) hormone
- GLUT 4 Receptors
  - Stimulated by insulin, **muscle contractions** and hypoxia – and *Alpha Lipoic Acid**
  - Major stimulus in GLUT4 expression is exercise!

Exercise and GLUT4 Receptors

- If GLUT4 receptors are responsible for glucose transport into muscles and it is known that exercise up-regulates GLUT4 expression, can we not apply this to diabetics??
- If an up-regulation of GLUT4 receptors is associated with exercise, wouldn't this up-regulation be associated with increased glucose utilization and thus better glycemic control in a diabetic??

- Ren, Jian-Ming. ***Exercise Induces Rapid Increases in GLUT4 Expression, Glucose Transport*** *Capacity and Insulin-Stimulated Glycogen Storage in Muscle*. Journal of Biological Chemistry. 1994(269) 14396-407.

- Three groups rats – 1 Day Swimmers & 2 Day Swimmers & Control
- Two 3 hour bouts swimming per day.
- Dissected forelimb muscle out and analyzed.
- Results: **1 day** swimmers had **2 fold increase in GLUT4 mRNA**
- 2 day swimmers had slight increase from 1 day swimmers
- 1 day swimmers had 55% increase in GLUT4 protein expression
- 2 day swimmers had 95% increase in GLUT4 protein expression
- Conclusion:
- **The rapid adaptation to exercise is to prevent hypoglycemia and fatigue during prolonged exercise. Exercise proves to be an effective stimulus of GLUT4 up-regulation.**

- Henriksson, H. *Exercise in the Management of Non-Insulin Dependent Diabetes Mellitus*. Sports Medicine. 1998,Jan 25 (1).

- Found that in healthy, non-diabetic individuals, exercise has little effect on blood glucose levels however in type 2 diabetics mod-high intensity exercise is associated with a decrease in blood glucose levels.
- Why? Poor hormone response in diabetics
- Insulin secretion decreases during exercise while glucagon elevates. Then how does glucose enter the skeletal muscle. **Muscle contractions stimulated GLUT4 receptors independent of insulin** which is important for diabetics with insulin resistance.

Microvascular Endothelial Dysfunction and DPN

- Theory of DPN related to decreased myelin bloodflow and microvascular dysfunction
- How can exercise improve endothelial function? NO-Dependent Vasodilation

Endothelial Vasodilation

- NO-dependent
  - Usually depressed in type diabetics
  - Free radicals scavenge NO - vasoconstriction
- Insulin-dependent
  - Vasodilation necessary for more rapid glucose uptake
  - Usually in long duration physical activity – increase in NO causing vasodilation – increased blood flow with faster glucose uptake
- Previous research in animals saw an increase in NO-dependent vasodilation and up-regulation of NO-synthase
- A 2001 study wanted to see if these effects could transfer to diabetic vascular function.

High Intensity RT is an Effective Means to Increasing NO-Dependent Vasodilation in Type II Diabetics

- Two groups – Exercise and Control Group
- 8 weeks, 1 hour, 3x week, **Circuit-Resistance Training, High Intensity**
- Results: **Flow-mediated dilation of brachial artery was significantly increased after exercise. This is an NO-dependent vessel.**
- **What was interesting was that all exercises were limited to the LE but the improved UE vasodilation suggests the NO-dilation effect is generalized.**

- Maiorana, Andrew. *The Effect of Combined Aerobic and Resistance Exercise Training on Vascular Function in Type 2 Diabetes.* Journal of American College of Cardiology. 2001 Sep; 38 (3): 860-6

Exercise-induced Vasodilation

- Benefits of exercise
  - Increased flow increased shearing stress to endothelium
  - Increased NO-synthase activity
  - Stimulated release of NO

RT for Older Diabetic Patients??

- Will older client with diabetes respond the same as younger client?
- Which is more appropriate, high intensity? Mod intensity?

A Progressive High Intensity RT Program is Well-Tolerated by Older Diabetics and is Shown to Improve Muscle Strength

- Two groups – 60 to 80 yo. **High intensity RT vs. Flexibility group**
- 6 months, 1 hour, 3x week
- ***1st 2 weeks 50-60% 1 RPM progressed to 75-85% 1 RPM**
- 3 sets, 8-10 reps, 90-120s between
- Results: Greater decrease in bp seen in RT group
- Focus was on the safety and tolerability of program on older age group.
- Conclusion: **Program was well-tolerated, effective at increasing muscle strength**

- ***Saw a 3x greater decrease in HbA1c – every 1% decrease is associated with 35% decreased risk of microvascular complications.**

- Dustan, David. *High Intensity Resistance Training Improves Glycemic Control in Older Patients with Type 2 Diabetes.* Diabetes Care. 2002, 25 (10).

Exercise is Effective at Preventing Peripheral Neuropathy in Type II Diabetics

Two groups – Exe + Control

4 year study, Brisk walking program

Results: **Peroneal n. NCV increased in Exe group and decreased in control group.**

Significant improvement of hallux VPT in Exe and diminished in control.

17% of Control developed PN – 0.0% of Exe group developed PN

Conclusion: **Long-term aerobic training (i.e. walking) can prevent the natural onset of PN in type II diabetics. Was probably associated to exercise-induced vasodilation.**

*Note that researchers chose brisk walking as it is easily reproducible to general diabetic population.

Balducci, S. *Exercise Training can Modify the Natural History of Diabetic Peripheral Neuropathy*. Journal of Diabetes and its Complications. 2006 20(4), 216-223.

DPN and Fall-Risk

- Shown by 1992 study that PN is an independent risk-factor for falls and that diabetic with PN is **15X more likely to fall** and report injury.
- What can we as fitness professionals do to prevent falls in diabetics?
  - Balance training, Flexibility, Strengthen ankle joint

Balance Training to Reduce Falls in Diabetic

2003 study showed enhanced **balance training** in 60+ year olds showed significant improvement in walking speed and confidence.

2004 study showed 5 weeks of **wobble board** showed improvement in ankle inversion movement discrimination (predictor of fall-risk).

2005 study showed 10 weeks, 3 x week of **agility training** resulted in faster ankle reflexes, improved balance and fewer falls.

APMSA Research Grant.

- **Purpose:** To determine the effectiveness of either balance training or strength training at improving the stability and reducing falls associated with diabetic peripheral neuropathy.
- **Methods:** A pilot study involving four (4) subjects with electromyographically-documented diabetic peripheral neuropathy and a self-reported history of instability and falls. Participants will be randomly divided into groups of 2 and assigned to either the balance training (group1) or the strength training (group 2). Each group will train with with the Primary Investigator, certified personal trainer, 2x a week for 30 minutes and a third day at home on their own for 30 minutes for a total of 6 weeks.
- Participants will be assessed for stability and balance before the study and immediately after the 6 weeks. Outcome measures will be include: (1) unipedal stance time – both with eyes open and closed, (2) tandem Romberg test – eyes open and closed, (3) 10 foot tamdem walk stability, and (4) a self-reported fall log.
- **Results:** We hypothesize that 6 weeks of either balance training or strength training will show improvement in stability and coordination of gait. We believe the greatest increase in stability will be associated with the balance training due to the direct incorporation of the visual and vestibular systems. We believe that strength training of the ankle stabilizing and core muscles will be associated with an increase in ankle joint stability and center of mass control.
- **Conclusions:** Dependent upon results and our proposed hypothesis, we hope to conclude that both balance training and strength training are effective interventions in reducing falls and increasing stability in patients with diabetic peripheral neuropathy. And that the best fall reduction program should incorporate both modalities.

In Summary...

- Exercise is an effective means of controlling blood sugar through the upregulation of skeletal GLUT 4 receptors.
- The control in blood glucose will prevent auto-oxidation and oxidative stress associated with DPN
- If DPN is already present exercise can prevent the progression of nerve damage through glycemic control
- If present symptoms include instability then balance training and resistance training can increase gait stablility

Thanks!!

ANY QUESTIONS??

Special Thanks to the New York State Podiatric Association