Exercise for Diabetic Neuropathy: A Paradigm Shift

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Disclosure

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Session Learning Objectives

After this session, you will be able to:

• Recognize symptoms of peripheral neuropathy in your patients
• Identify clinical measures to screen for the presence of neuropathy, assess the severity of neuropathy, or monitor changes to assist with clinical decision making.
• Review the current evidence from animal models that supports how exercise protects and/or reverses peripheral nerve dysfunction in the prediabetic/diabetic state.
• Understand the clinical applicability of exercise for individuals with DPN relative to cutaneous innervation and the potential impact on clinical balance measures, muscle strength, pain, and ultimately neuropathy-specific quality of life.
Session Learning Objectives (continued)

After this session, you will be able to:

- Summarize the musculoskeletal impairments and physical performance deficits that are commonly observed in individuals with diabetes mellitus and peripheral neuropathy that will serve as basis for intensity-based, multi-component exercise training to remedy these impairments and deficits.

- Understand how to monitor and progress appropriate overload stress for the person with DPN who may lack sensory (pain) feedback.

- Recognize the potential positive effect of exercise on the patient-centered outcomes of pain, pain interference, fatigue, and fatigability for people with DPN
What is neuropathy?
How should we screen for it?
How should we assess it?

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Diabetes mellitus: a primer

Insulin = allows transport of glucose across cellular membrane
- Type 1 DM: autoimmune pancreatic deficiency, not enough insulin (5-10%)
  → Glucose unable to enter cells
- Type 2 DM: tissues insulin resistant (90-95%)
  → Glucose unable to enter cells

Hyperglycemia
Impaired Glucose Tolerance

• “Pre-diabetes”
• Moderate hyperglycemia – how measured?

<table>
<thead>
<tr>
<th></th>
<th>Fasting glucose test</th>
<th>Oral glucose tolerance test (2hours post)</th>
<th>HbA1c</th>
</tr>
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<tbody>
<tr>
<td>Normal</td>
<td>&lt;100 mg/dl</td>
<td>&lt;140 mg/dl</td>
<td>&lt;6%</td>
</tr>
<tr>
<td>IGT</td>
<td>100-125 mg/dl</td>
<td>140-200 mg/dl</td>
<td>6.0-6.4%</td>
</tr>
<tr>
<td>T2D</td>
<td>&gt;126 mg/dl</td>
<td>&gt;200 mg/dl</td>
<td>&gt;6.5%</td>
</tr>
</tbody>
</table>
High Risk of Diabetes ...

- IF overweight (BMI > 25 kg/m²) AND

<table>
<thead>
<tr>
<th></th>
<th>Sedentary</th>
<th>African-American, Latino, Asian American, Native American</th>
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</thead>
<tbody>
<tr>
<td>45 or older</td>
<td>Sedentary</td>
<td>African-American, Latino, Asian American, Native American</td>
</tr>
<tr>
<td>GDM or gave birth to baby &gt;9 lbs</td>
<td>HTN (&gt;140/90 or on meds)</td>
<td>HDL cholesterol &lt;35 or triglyceride &gt;250</td>
</tr>
<tr>
<td>Polycystic Ovary Syndrome (PCOS)</td>
<td>1st degree relative with DM</td>
<td>Cardiovascular disease</td>
</tr>
</tbody>
</table>
Diabetic Peripheral Neuropathy

• Present in 2/3 of people with T1D and T2D
• Symmetric, sensory, poly neuropathy
  – most common type
  – painful and non-painful phenotypes

<table>
<thead>
<tr>
<th>Large Fiber Neuropathy</th>
<th>Vibration, proprioception, hyporeflexic, paresthesia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small Fiber Neuropathy</td>
<td>Pain, dysesthesia, allodynia</td>
</tr>
</tbody>
</table>
Physical Activity Recommendations

Adults with diabetes should engage in:
1. >150 min/week aerobic (50-70% max HR)
2. Reduce sedentary time (>90 minutes sitting)
3. Resistance training > 2 times each week

IF DPN:
Proper footwear
Examine feet daily
If lesion ➞ non weight bearing exercise
Screening for DPN

“All patients with diabetes should be screened annually for DPN starting at diagnosis”

• Simple clinical tests:
  – 10 g monofilament
  – Ankle reflexes
  – Vibration threshold (128 Hz tuning fork)

  – Symptoms: pain, dysesthesia, numbness
Treatment for DPN

• Glycemic control: prevent, delay, slow progression of DPN
• Pharmacological agents for pain: pregabalin duloxetine, tapentadol, others

Need new, targeted approach!
Emerging research on exercise …
Prediabetic/Diabetic Animal Models Evidence to Support How Exercise Protects Against Diabetic Peripheral Neuropathy

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Assistant Professor, Physical Therapy
College of Allied Health Sciences
East Carolina University
Greenville, NC
Rise in Diabetes/ Obesity Rates….

- Lead to a significant rise in diabetic peripheral neuropathy (DPN)
- DPN is the most prevalent complication of diabetes (Boulton et al. 2005)
- Strong correlation between risk factors for vascular disease and the development of DPN
- Nervous system is particularly vulnerable to effects of diabetes/obesity

www.cdc.gov/
Highest Prevalence of Diabetes and Obesity: Southern US

www.cdc.gov/
Why Use Animal Models?

- Ability to probe the mechanism behind the development of diabetes, obesity, and diabetic peripheral neuropathy
- Assess initial efficacy and safety of pharmaceutical and non-pharmaceutical approaches, as well as the mechanisms of these treatments
- Extensively used in the field of diabetes and obesity research
- Significant advances in the field can be attributed to animal research including the discovery of insulin
Animal Models of Diabetes and Obesity

**Type 1 Diabetes:**
- Spontaneous
- Drug induced pancreatic beta cell toxicity
  Streptozotacin (STZ)

**Type 2 Diabetes:**
- Dietary induced
  Animals fed high fat & or high sucrose – “*Western style diet*”
- Genetic

Widely used in diabetes/obesity research as well as to study DPN
Diabetic Peripheral Neuropathy (DPN) Pathogenesis

- **Insulin Deficiency** → **Hyperglycemia**
- **Initiating Events**
- **Metabolic Changes**
  - Polyol Pathway
  - Inflammation
  - Paraldehyde (PARP)
  - Advanced Glycation End Products (AGEs)
  - Hexosamine Pathway
  - Mitochondrial Dysfunction
- **Altered Neurotrophism** → **Oxidative Stress**
- **Physiologic/Morphologic Changes**
  - Nerve Conduction Velocity
  - Neuropathic Pain
  - Psychosensory Sensation
  - Axonopathy
  - Microvascular Damage
  - Intra-Epidermal Nerve Fiber Density
  - Myelin Thinning

Farmer et al. 2012
DPN Targets: Sensory Neurons

• Primary afferent (sensory) neurons and their cell bodies (dorsal root ganglia, DRG) are uniquely sensitive to damage (McHugh et al. 2004, Zochodne 2001, 2007)

• Present as “positive symptoms” of pain (burning/tingling) or “negative symptoms” (numbness or altered proprioception)
DPN: Neurodegeneration

- “Dying back” disorder
- Animal models support that this is the loss of the distal axon before neuronal death (Cheng and Zochodne 2003, Russell et al. 1999, Zochodne 2001)
- Axons and sensory neuron atrophy accompanied by loss of epidermal skin axons
- “Double hit” neurodegeneration and reduced regeneration (Kennedy and Zochodne 2002, Kalichman et al. 1998)

Metabolic dysregulation
Pain
Nerve conduction changes
Loss of epidermal innervation
Loss of axon (distal/central)
Cell body atrophy
Further axonal loss
Irretrievable neuron loss
Experimental DPN: Epidermal Innervation

- Diabetic mice that spontaneously recover show improved epidermal reinnervation, without improvement in neuronal loss (Kennedy et al. 2000, 2003, Zochodne 2007)

- Collateral reinnervation/regeneration from preserved sensory neurons might be associated with clinical recovery

Zochodne 2007
Exercise as Therapy for DPN
Evidence From Experimental Type 1 Diabetes

- Exercise delayed the onset of mechanical hypersensitivity independent of glucose control
- Exercise reduces changes in Ca$^{2+}$ function to improve electrophysiological deficits in DPN (Shankarappa et al. 2011)
- Reduces myelin loss in DPN (Selagzi et al. 2008)

Shankarappa et al. 2011
Exercise Improves Nerve Regeneration in Experimental Type 1 Diabetes

- Nerve regeneration after injury is impaired in diabetes (Kennedy and Zochdne 2000)

- Emerging evidence from experimental diabetes show that exercise (moderate intensity) improves sciatic nerve regeneration (Malysz et al. 2010), decreases target muscle atrophy (Malysz et al. 2011)
Pain: An Early Warning Sign of Peripheral Neuropathy

• **Pain** is an *early and predominant* symptom of DPN in humans and animal models (Boulton et al. 2005, Feldman et al. 2005)

• Neuropathic pain symptoms described as burning, tingling, crawling, pins and needles can be severe despite minimal signs of DPN, often presenting before a diagnosis of diabetes

• Current therapies targeting painful symptoms in patients are largely ineffective
High Fat Diet (HFD) Induces Prediabetes and Neuropathy

• Elevated oxidative stress and inflammation in DRG and peripheral nerves (Ozay et al. 2014, Obrosova et al. 2007)

• HFD significantly reduced axon size and myelin diameter (Ozay et al. 2014)

• Sensory and motor nerve conduction deficits (Obrosova et al. 2007)

• Tactile allodynia/ hyperalgesia in the absence of epidermal nerve fiber loss (Obrosova et al. 2007, Groover et al. 2013)
Exercise Reduces Oxidative Stress Induced by a High Fat/High Sucrose Diet

<table>
<thead>
<tr>
<th></th>
<th>Glucose (mg/dl)</th>
<th>Insulin (pM)</th>
<th>HOMA-IR</th>
<th>HNE-Adducts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>115 ± 2.9</td>
<td>126.7 ± 33.4</td>
<td>5.06 ± 1.36</td>
<td>0.70 ± 0.09</td>
</tr>
<tr>
<td>4 week</td>
<td>105 ± 4.8</td>
<td>87.1 ± 15.0</td>
<td>3.19 ± 0.66</td>
<td>0.75 ± 0.23</td>
</tr>
<tr>
<td>8 week</td>
<td>110 ± 3.3</td>
<td>159.8 ± 30.4</td>
<td>6.03 ± 1.09</td>
<td>0.98 ± 0.14</td>
</tr>
<tr>
<td>12 week</td>
<td>131 ± 3.5</td>
<td>155.8 ± 14.0</td>
<td>7.02 ± 0.62</td>
<td>1.20 ± 0.15</td>
</tr>
<tr>
<td>12 week + EX</td>
<td>109 ± 3.7</td>
<td>116 ± 23.4</td>
<td>4.51 ± 1.09</td>
<td>0.41 ± 0.06</td>
</tr>
</tbody>
</table>

Bareiss et al. *in preparation*
Exercise Normalizes Hypersensitivity and Altered Neurotrophin Expression in Prediabetic Animals

Groover et al. 2013
Exercise Restores Normal Epidermal Innervation in a Prediabetic Model

- Prediabetic animals show no reductions in total epidermal innervation (Groover et al. 2013, Obrosova et al. 2007)

- Epidermal phenotype – relative increase NGF/nociceptive responsive epidermal fibers

Groover et al. 2013
Diabetic Peripheral Neuropathy (DPN) Pathogenesis

Initiating Events

Metabolic Changes

Physiologic/Morphologic Changes

Insulin Deficiency

Hyperglycemia

↑ Polyol Pathway

↑ Inflammation

↑ PKC Activity

↑ PARP

↑ AGEs

Hexosamine Pathway

↑ Mitochondrial Dysfunction

↓ Nerve Conduction Velocity

↑ Neuropathic Pain

↓ Psychosensory Sensation

↓ Axonopathy

↑ Microvascular Damage

↓ Intra-Epidermal Nerve Fiber Density

↑ Myelin Thinning

Exercise

Farmer et al. 2012
Summary: Animal Studies Support Exercise to Protect/Reverse Symptoms Associated with DPN

- Prediabetes and diabetes results in alterations in both the peripheral nerve and DRG
- Exercise decreases DPN symptoms and damage to peripheral nerves in multiple diabetic/prediabetic models
- Putative mechanisms – restoring neurotrophin levels, reductions in oxidative stress, improve Ca+ dysregulation, other factors that promote nerve regeneration and preserve/restore neuronal function
- Supports the prescription of aerobic exercise to prevent and reduce DPN symptoms associated with prediabetes/diabetes
References

Impact of Exercise on Cutaneous Reinnervation and Patient-Centered Functional Outcomes

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Salt Lake City, Utah
Marcus Disclosure

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• NIDDK R21 DK099393-01A1
• NCATS 1ULTR001067
Why is this important to physical therapists?

Neuropathy is present in 2/3 of people with diabetes and is associated with metabolic syndrome.

Kirkness, Marcus, LaStayo et al., 2008, Physical Therapy
Neuropathy pathogenesis

Insulin resistance → ↑FFAs → hyperglycemia → adipokines → Obesity, dyslipidemia

↑TNF-α/ceramide → NADPH depletion → eNOS inhibition → ↓NO → endothelial injury

↑ROS → ROS detoxification → reduced vascular reactivity

FA oxidation → polyol pathway → transition metals → AGEs

immune activation → direct nerve injury
Rational therapies

- Insulin resistance
  - ↑FFAs
  - hyperglycemia
- Obesity
  - adipokines
- ARIs
  - FA oxidation
  - polyol pathway
  - transition metals
- ALA
  - NADPH depletion
  - ROS detoxification
- PGE1
  - immune activation
- Immuno-suppression
- ACE inhibitors
  - endothelial injury
  - reduced vascular reactivity
  - direct nerve injury
- Immuno-suppression
- aminoguanidine

- TNF-α/ceramide

- Immuno-suppression

- CSM 2015

- University of Utah College of Health
  Department of Physical Therapy
Clinical trials

“Discouraging data on the antidepressant.”
Does exercise work?

- Aerobic, resistance exercise improves physical fitness, glycemic control and insulin sensitivity in those with diabetes Davidson 2009; Larose 2010; Sigal 2007, Colberg 2010

- “Lifestyle” interventions that include diet and exercise can reduce the prevalence of diabetes and its complications, including neuropathy Knowler 2002, Nathan 2005; Orchard 2005

- There is a lack of high quality evidence to evaluate the effect of exercise in people with peripheral neuropathy - Cochrane Review White 2004, updated in 2010, but since 2010

In those with DPN.....exercise improves balance Streckman 2014, trunk proprioception, strength, Song 2011, Nardone 2010 6MW distance, habitual physical activity Mueller 2013 and more.....
Exercise prevents neuropathy?

“Progression to neuropathy”

Clinical motor neuropathy

Clinical sensory neuropathy

Reduced vibration threshold

Balducci, J Diab Comp 2006
How is nerve function measured?

• Neuropathy associated with metabolic syndrome features often causes prominent **small fiber injury**
• Regenerative capacity of small axons offers promising therapeutic targets
• Skin biopsy with quantification of intraepidermal nerve fiber density (IENFD) is reliable to confirm the diagnosis of small fiber neuropathy
• IENFD declines early in DPN and is responsive to treatment
• IENFD = # of intraepidermal nerves per unit area of skin
• Average IENFD decreases distally – common areas are proximal thigh (10cm distal to greater trochanter) and distal leg (10cm proximal to lateral malleolus)
Improved metabolic function significantly improves IENFD in Pre-Diabetic Neuropathy

Smith, Singleton, *Diabetes Care* 2006
• Lifestyle Intervention
  – Diabetes Prevention Program
    • Intensive training in diet, physical activity, and behavior modification
      – weight loss of 7% of initial body weight
      – moderate physical activity of ~150 minutes/week

• Resistance Exercise
  – ACSM & ADA: joint position statement executive summary of Exercise and Type 2 Diabetes Colberg 2010
    • 2x weekly resistance training in the absence of contraindications

Neuropathy pathogenesis

- Obesity, dyslipidemia
- Adipokines
- Exercise

ExERCISE

- Insulin resistance
- 
  - ↑ TNF-α/ ceramide
- NADPH depletion
- FA oxidation
- Polyol pathway
- Transition metals
- AGEs
- Immune activation
- Direct nerve injury
- Reduced vascular reactivity
- Endothelial injury
- NO
- ROS
- ROS detoxification
- eNOS inhibition

COMBINED SECTIONS MEETING OF THE AMERICAN PHYSICAL THERAPY ASSOCIATION
How does exercise work?

EXERCISE → Neuropathic Pain → Quality of Life
EXERCISE → Sensory Loss → Quality of Life
EXERCISE → Muscle Function → Quality of Life
EXERCISE → Mood & Sleep → Quality of Life
EXERCISE → Gait & Balance → Quality of Life
EXERCISE → Mobility → Quality of Life

Streckman et al, Sports Med 2014
White et al., Cochrane Review 2004, 2010
Is exercise safe?

- Leg-strengthening, balance and walking exercise does not increase fall incidence in those with DPN Kruse 2010
- No serious adverse events, pain or neuropathic symptoms after 12 or 16 week exercise program in those with DPN Kluding 2012, 2014 Some minor adverse events requiring physical therapist intervention Kluding 2014

MONITORING IS CRITICAL
Exercise improves IENFD and neuropathy symptoms in diabetic neuropathy

- Supervised exercise 3-4x/wk for 10 weeks, n=17
  - HbA1c declined 7.8% to 7.1%
  - 30% decline in pain severity
  - Improvement in neuropathy severity score
  - ↑ epidermal nerve fiber branches

Results suggest exercise may have important effects on nerve regeneration

K luding et al, J Diab Compl. 2012
(Successful) Lifestyle Intervention Results in Improved Nerve Regenerative Capacity

- Supervised exercise + diet counseling 2x/wk, 6 mos, n=36 T2D or met syndrome, no neuropathy
  - Baseline regeneration rate is reduced
  - Significant ↑ in cutaneous reinnervation following intervention
  - Greatest change in reinnervation rate present in those with most metabolic syndrome features improved
Supervised exercise improves IENFD in patients with diabetes

- Supervised exercise + diet counseling, weekly for 12 mos, n= 53 patients with T2D, no neuropathy
  - Significant ↑ in cutaneous reinnervation
  - Compliance issues?

Singleton, Marcus, Jackson et al., 2014, *Annals of Clinical and Translational Neurology*
Exercise and type 2 diabetes: New prescription for an old problem
Stephen R. Bird, John A. Hawley
*Maturitas* 2012

“there is an urgent need for innovations in exercise prescription that can be incorporated into daily living and induce clinically beneficial health outcomes”

- >30% of type 2 diabetic patients fail to participate in basic physical activity  Nelson 2002
- 65% of type 2 diabetic patients dropped out of a 1 year walking program  Praet 2008
Increased active time

- 10 subjects with DPN
- 8 week pilot
- 2x weekly supervised exercise
- Motivational interviewing, daily text messages/calls
Some unanswered questions…

• Can we impact nerve function with exercise that is **sustainable** in patients with neuropathy?

• If so, does this also have a clinically meaningful impact on **patient-centered outcomes** – mobility, balance and quality of life?

• Is there an **adverse impact** on skin condition, falls?

• What is the **appropriate dosage** to accomplish the effect?
Summary of Exercise Impact on Cutaneous Reinnervation and Patient Centered Outcomes

• Patients with diabetes and metabolic syndrome are commonly seen by physical therapists
• DPN can occur early in diagnosis – this is when it may be most amenable to the effects of exercise
• Aerobic, resistance, and balance exercise all have positive effects on patient-centered outcomes – minimal side effects
• Exercise impacts nerve regeneration in animals, evidence is emerging for humans – linked to metabolic improvement
• Whether the nerve changes mediate improved patient-centered outcomes is currently unknown
• Highlights the need for physical therapists to encourage exercise participation in this patient population
• Compliance issues suggests creative, novel approaches are necessary – and monitoring is critical
Musculoskeletal Impairments & Physical Performance Deficits in Individuals with Diabesity & Peripheral Neuropathy: Basis for Multi-Component Exercise Training.

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Sinacore Disclosure

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- NIA P60 AG 13629    1995-2000
- NIA R01 AG 15795    1998-2003
- NIDDK R01 DK 059224  2000-2004
- NIA R01 AG 025501    2005-2009
- NIDDK R21 DK 079457  2007-2010
- NICHD R03 HD 068660  2012-2014
- NIA R01 AG 049369    2014-2019
‘DIABESITY’ in U.S.

“TWIN” Epidemics of OBESITY & DIABETES MELLITUS in the ‘1990’s merge into ‘DIABESITY in the New Millenium as ...

PUBLIC HEALTH ENEMY #1
DIABETES MELLITUS in the New Millenium: From SARCOPENIA to DIABESITY & Back?

THEN
(Prior to 1921)

NOW
(Diabesity !!)

SARCOPENIA !!

SARCOPENIA ??
Modified Physical Performance Test (PPT)  

• 50 foot walk with turn
• lift book to shelf overhead
• put on/take off with jacket
• pick up penny from floor
• turn 360 degrees- both ways!
• standing balance-eyes open
• chair rise 5x- 16” chair height
• climb 1 flight of stairs
• climb 4 flights of stairs
‘Perfect’ Score = 36 points

FRAILTY CLASSIFICATION based on mPPT scores

**Severe**
PPT: ≤ 21
< 25th Percentile

**Moderate**
PPT: 22 – 29
25th – 75th Percentile

**Mild to None**
PPT: 30 – 36
75th – 100th Percentile
DXA for Whole-Body Composition

<table>
<thead>
<tr>
<th>Region</th>
<th>Fat (g)</th>
<th>Lean+BMC (g)</th>
<th>Total (g)</th>
<th>%Fat (%)</th>
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<tbody>
<tr>
<td>L Arm</td>
<td>3750.4</td>
<td>2308.0</td>
<td>6058.5</td>
<td>61.9</td>
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<tr>
<td>R Arm</td>
<td>2752.7</td>
<td>1605.3</td>
<td>4358.0</td>
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<td>30004.3</td>
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<td>9904.0</td>
<td>8461.0</td>
<td>18365.0</td>
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<td>Sub Tot</td>
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<td>52122.6</td>
<td>113771.4</td>
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<tr>
<td>Head</td>
<td>897.7</td>
<td>3525.4</td>
<td>4423.1</td>
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<td>62546.5</td>
<td>55647.9</td>
<td>118194.5</td>
<td>52.9</td>
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</table>

TBAR2802
F.S.  68.00%  -10.00%
Head assumes 17.0% brain fat
LBM 73.2% water

Discovery Wi  SN: 80039
Version 12.01  08/27/2007 14:52

CSM 2015
SARCOPENIA defined by Skeletal Muscle Mass

Skeletal Muscle Index or Relative Skeletal Muscle Index

SMI or RSMI -2 SD BELOW the sex-specific value

• Men:  < 37% SMI  
< 7.26 kg/m² RSMI

• Women: < 28% SMI  
< 5.45 kg/m² RSMI

MRI (or CT) for Regional Body Composition

Sarcopenic Obese, Frail, Older Adult

Non-Sarcopenic, Non-Frail Adult
Physical Frailty & Sarcopenia in Obese Adults with T2DM & PN

Physical Performance Test Score vs. Skeletal Muscle Index (%)

- Obese Control
- T2DM
- T2DMPN

Percentile Categories:
- Severe: 0 to 25th Percentile
- Moderate: 25th to 75th Percentile
- Mild to None: 75th to 100th Percentile

Bittel DC et al. J Frailty & Aging 2015 (Abstract)
Physical Frailty & Sarcopenia Classifications in Obese Adults with T2DM PN

Bittel DC et al. J Frailty & Aging 2015 (Abstract)
Leg % IMAT & Sarcopenia in Obese Adults with T2DM PN

Intermuscular Adipose Tissue (%) vs. Skeletal Muscle Index (%)

- Women
- Men

Non-sarcopenic
Sarcopenic

Bittel AJ et al. Physical Therapy 2014 (In Review)
Leg % IMAT & Sarcopenia in Obese Adults with T2DM PN

WOMEN

MEN

Skeletal Muscle Index (%) vs. Intermuscular Adipose Tissue (%)

Sarcopenic vs. Non-sarcopenic

Women: ◦
Men: ▲

Non-sarcopenic
Sarcopenic

%IMAT cutoff (21%)
Plantar Flexor Peak Torque & Sarcopenia in Obese Adults with T2DM PN

Bittel AJ et al. Physical Therapy 2014 (In Review)
Plantar Flexor Peak Torque & Sarcopenia in Obese Adults with T2DM PN

WOMEN

MEN

Skeletal Muscle Index (%)

Plantar Flexion Torque (Nm)

Plantar Flexion Torque cutoff (68 Nm)

Bittel AJ et al. Physical Therapy 2014 (In Review)
Progressive Movement Impairment during heel rise-plantar flexion in sarcopenic diabesity

GOOD  BAD  UGLY
39.4 % Body Fat; BMI=28.4
Leg Total Fat: 333 cm³
SQAT: 310 cm³
IMAT: 23 cm³
%SQAT = 93
%IMAT = 7
Gastroc-Soleus% volume= 65
9-item PPT Score: 35

45.1% Body Fat; BMI=37.9
Leg Total Fat: 305 cm³
SQAT: 226 cm³
IMAT: 79 cm³
%SQAT = 74
%IMAT = 26
Gastroc-Soleus% volume= 60
9-item PPT Score: 32

30.7 % Body Fat; BMI=37.2
Leg Total Fat: 330 cm³
SQAT: 185 cm³
IMAT: 145 cm³
%SQAT = 56
%IMAT = 44
Gastroc-Soleus% volume= 52
9-item PPT Score: 30

GOOD
Control participant

BAD
T2DM-only participant

UGLY
T2DMPN participant
Stair Power & Sarcopenia in Obese Adults with T2DM PN

Bittel AJ et al. Physical Therapy 2014 (In Review)
Stair Power & Sarcopenia in Obese Adults with T2DM PN

WOMEN

MEN

Skeletal Muscle Index (%)

Stair Power (Watts)

Sarcopenic

Non-sarcopenic

440 Watts

Women

Men

Non-sarcopenic

Sarcopenic

Stair Power cutoff (440 Watts)

Bittel AJ et al. Physical Therapy 2014 (In Review)
Limited Joint Mobility in Diabesity & Peripheral Neuropathy

- Systemic impairment
- Multiple joints affected: hands, wrist, shoulders, AJ, STJ, MTPJs
- Advanced Glycation End Products (AGEs)

+ ‘Prayer’ Sign

- First MTPJ
  - Hallux Limitus: Ulcer 1st toe
    - Birke et al, JOSPT, 1988
- STJ
  - Midfoot Deformity
    - Sinacore et al, JFAR 2013
- AJ
  - Hind foot Deformity
    - Sinacore et al, JFAR 2013
Recap of Musculoskeletal Impairments & Physical Performance Deficits in Diabesity & Peripheral Neuropathy

1. Diabesity = Obesity & T2DM

2. Sarcopenia- Loss in leg muscle quality; XS IMAT accumulation.

3. Dynapenia- ‘extrinsic’ muscle strength & power impairment (DF & PF); impaired heel rise foot deformities

4. Reduced Stair Power; reduced chair rising, stair climbing

5. Limited Joint Mobility; foot, ankle, shoulder, hand, wrist.

Early Physical Frailty & Disability
Multi-Component Exercise Training
High-Intensity Progressive Resistance Training
References


Effect of overload stress on the neuropathic foot: adaptation or breakdown?

Mary K. Hastings, PT, DPT, MSCI
Washington University School of Medicine
St. Louis MO
Injury due to *excessive* physical stresses

Pre-Exercise Screening

• Peripheral Neuropathy
  – Semmes Weinstein Monofilament (5.07)
  – Implications + peripheral neuropathy
    • Frequent foot inspections
      – Especially when starting new exercise program
    • Always wear footwear
      – Includes in the house, pool, beach

• Skin
  – Callous: Location, color, size
    • Implications: indicator of stress
      – Need for change in footwear/insoles
      – If + peripheral neuropathy recommend professional foot care (nails, callus)
  – Wound
    • Implications:
      – Weightbearing surface: weightbearing exercise contraindicated
  – Red area (particularly weightbearing or contact surface)
    • Implications: indicator of friction or inflammation
      – examine footwear/insoles/deformity
  – Dry/fissures
    • Implications: Need for lotion and professional management
      – avoid open wound…site of infection
Foot Deformities and Implications

• Forefoot
  – Prominent metatarsal heads

• Midfoot

• Key
  – Site of high stress: skin breakdown/fractures
  – Site of structural instability: fractures/dislocation
  – Question: can stress be maintain below the injury threshold for the all tissue
  – Options
    • Footwear/Insoles
    • Non-weightbearing activity
    • Slow progressive weightbearing activity
      – increasing tissues’ tolerance to stress level
Footwear

- Correct Length and Width (especially the toe box)
- Total Contact Insert if Indicated
- Doesn’t Slip or Rub during Movement
  - Tie shoe preferred
- Foot Enclosed
  - Avoid open toes, sandals
- Waterproof
  - Swimming/water aerobics
  - Shower shoes
History and Other Concerns

- **History of ulcer**
  - Predictor of future ulcer

- **Blood sugar**
  - Measure every visit and modify exercise as required
  - Current level
    - Implications:
      - **>250 mg/dl**
        - Implications: check Ketones in urine, postpone exercise
      - **<100 mg/dl**
        - Ingest carbohydrate
  - Control (Hemoglobin A1c)
    - **<7**
    - Implications for exercise: blood sugar is not being well controlled, frequent blood sugar monitoring maybe required (before, during and after)

- **Blood Pressure**
  - Measure every visit and modify exercise as required
  - Are they taking their medication?

<table>
<thead>
<tr>
<th>CATEGORY</th>
<th>SYSTOLIC</th>
<th>DIASTOLIC</th>
<th>ACTION TAKEN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;120</td>
<td>&lt;80</td>
<td>None</td>
</tr>
<tr>
<td>Prehypertension</td>
<td>120-139</td>
<td>80-89</td>
<td>Educate patient</td>
</tr>
<tr>
<td>Hypertension:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Stage I</td>
<td>140-159</td>
<td>90-99</td>
<td>Call MD before next visit</td>
</tr>
<tr>
<td>- Stage II</td>
<td>≥160</td>
<td>≥100</td>
<td>Call MD this visit.</td>
</tr>
<tr>
<td>- Stage III</td>
<td>&gt;180</td>
<td>&gt;110</td>
<td>Hypertensive Crisis</td>
</tr>
</tbody>
</table>
References

- American Diabetes Association:
  - Clinical Practice Recommendations, January 2015
  - The Journal of Clinical and Applied Research and Education, 38:supplement 1;

- American Heart Association:
  - http://www.heart.org/HEARTORG/Conditions/HighBloodPressure/AboutHighBloodPressure/Understanding-Blood-Pressure-Readings_UCM_301764_Article.jsp
Effect of overload stress on the neuropathic foot: adaptation or breakdown?

• Michael J. Mueller, PT, PhD, FAPTA

• Disclosures
  – National Center for Medical Rehabilitation Research, NIH, R21HD058938.
  – Foundation for Physical Therapy (Lori Tuttle)
  – No other conflicts of interests to report
Higher step count in those without skin breakdown

- Maluf & Maluf, 2002
- LeMaster et al, 2003
- Armstrong et al, 2004

DM+PN, age 70, SWM>6.10
16,000 step/day (8,000 strides)
Is neuropathic skin / foot adaptable?

Ho: Yes, but “small window of adaptation” and need to consider carefully co-morbidities
“Feet First” Study: Community based home exercise program. LeMaster et al, PTJ, ‘08

Pts: DM+PN, n=41 Intensive; 38 in standard group, mean age 66; Tx: 8 1-1 sessions Over 3 months to teach personal program including walking for intervention group.

No difference in incidence of foot lesions.

Small changes

Total steps per day, all subjects
Weight Bearing vs. Non-Weight Bearing Exercise for People with DMPN: A Randomized Controlled Trial

266 Contacts
↓
29 Randomized
↓
Weight-Bearing Group; n=15
↓
12 week intervention
↓
Post-test; n=15

Non-Weight-Bearing Group; n=14
↓
12 week intervention
↓
Post-test; n=14

Primary Outcome Variables
- Six Minute Walk Distance
- Average Daily Step Count

Mueller et al, APMR, 2013
Progressive balance, flexibility, strengthening, and aerobic exercise

Goal: 30 minutes of moderate activity per day (American Diabetes Association)

INTERVENTION: 3 x/week for 12 weeks; Moderate Intensity: 60-70% of age-predicted max heart rate; RPE =11-13 on a 6-20 scale.

Non-weight-bearing

Weight-bearing

Balance Exercises

Strengthening Exercises
Aerobic Exercise

Duration based on participants own average step count – increase 10% every 2 weeks

Non-weight-bearing  Weight-bearing
## Between group differences (Improvements) over time

<table>
<thead>
<tr>
<th>Primary Variables</th>
<th>Group</th>
<th>Pre-test Mean (SD)</th>
<th>Post-test Mean (SD)</th>
<th>Between Group Difference Mean (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 minute walk</td>
<td>WB</td>
<td>378 (72)</td>
<td>404 (78)</td>
<td>29 (6 to 51)</td>
</tr>
<tr>
<td>Distance (meters)</td>
<td>NWB</td>
<td>418 (106)</td>
<td>417 (112)</td>
<td>29 (6 to 51)</td>
</tr>
<tr>
<td>Average Daily Step Count (steps)</td>
<td>WB</td>
<td>4909 (1398)</td>
<td>5593 (1449)</td>
<td>1178 (150 to 2205)</td>
</tr>
<tr>
<td></td>
<td>NWB</td>
<td>6571 (2186)</td>
<td>6078 (2023)</td>
<td>1178 (150 to 2205)</td>
</tr>
</tbody>
</table>

## Secondary Variable

<table>
<thead>
<tr>
<th>Glycated Hemoglobin (HbA1c, %)</th>
<th>Group</th>
<th>Pre-test Mean (SD)</th>
<th>Post-test Mean (SD)</th>
<th>Between Group Difference Mean (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WB</td>
<td>6.9 (1.3)</td>
<td>7.0 (1.3)</td>
<td>0.50 (0.03 to 0.96)</td>
<td></td>
</tr>
<tr>
<td>NWB</td>
<td>7.8 (2.1)</td>
<td>7.4 (1.6)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Improved Dorsiflexion ROM
Knee Extended

Significant increase in WB and NWB groups at T2 compared to T1; p<0.05.

- No Significant Interactions

Error bars represent +/- Standard Deviation.
No changes in measures of Calf Muscle “Strength”

<table>
<thead>
<tr>
<th>Plantar flexor Peak Torque (Nm)</th>
<th>WB</th>
<th>33</th>
<th>36.90(14.80)</th>
<th>36.63(10.50)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NWB</td>
<td>36.90(14.80)</td>
<td>36.63(10.50)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Total Calf Muscle Volume (cm³)</th>
<th>WB</th>
<th>440.3(86.9)</th>
<th>432.2(102.3)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NWB</td>
<td>387.4(119.6)</td>
<td>384.6(121.8)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Total Calf Inter muscular adipose tissue (IMAT) Volume (cm³)</th>
<th>WB</th>
<th>0.231(0.196)</th>
<th>0.246(0.195)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NWB</td>
<td>0.185(0.119)</td>
<td>0.192(0.132)</td>
</tr>
</tbody>
</table>

Not adaptable or insufficient overload?
Groups showed some **improvements** over time in:

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group</th>
<th>Pre-test Mean (SD)</th>
<th>Post-test Mean (95% CI)</th>
<th>Within Group Time Difference Mean (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FAAM (0-100; %) WB</td>
<td>73.0 (21.6)</td>
<td>83.7 (12.5)</td>
<td>10.7 (1.8 to 19.5)</td>
<td></td>
</tr>
<tr>
<td>Overall Perception NWB</td>
<td>79.5 (16.8)</td>
<td>85.2 (13.7)</td>
<td>5.7 (-3.8 to 15.2)</td>
<td></td>
</tr>
<tr>
<td>Physical Performance</td>
<td>28.1 (4.6)</td>
<td>29.5 (4.9)</td>
<td>1.4 (0.04 to 2.8)</td>
<td></td>
</tr>
<tr>
<td>Test (9 item; 36 max)</td>
<td>27.1 (4.6)</td>
<td>28.7 (4.2)</td>
<td>1.6 (0.2 to 3.0)</td>
<td></td>
</tr>
</tbody>
</table>

Improved **gait speed**; 108 to 116 cm/s following 12 weeks aerobic exercise (Morrison S, et al 2014)

Small improvements in **TUG and 10-m walking time** with balance ex for 8 weeks, RCT (Song et al , 2011)

Generally, all improvements are small but that in contrast to expected decline.

Is neuropathic skin / foot adaptable?

• Unless tissue is “dead”, expect positive adaptations from stress (ex) overload
• Weight-bearing ex ok for mild deformity but monitor carefully
• Integrate activity into lifestyle that works for individual
• More research to define parameters of adaptation
What do patients care about?
Pain, QOL, Balance, and Fatigue outcomes

Patricia M Kluding, PT PhD
University of Kansas Medical Center
Kansas City, KS
What is the patient’s perspective?

• Feb 2014 Neuropathy Association’s Facebook Chat: “Staying Active with Neuropathy”
  • >500 chat participants
  • >5,000 views within 48 hours

I know that when I found this page it was some of my darkest hours of the morning in pain. And it's just nice to have a place to go where you can talk with people that have similar issues.

Thanks everyone - doctors, organizers, fellow NPers. Most informative and very definitely reinforces the helpfulness and importance of physical exercise, both physically and mentally!
Diabetic Peripheral Neuropathy is BAD!

What is it like to live with neuropathy?
- “I feel pins and needles in my feet”
- “My pain is severe and 24/7/365. It has taken my joy out of life.”
- “My feet are numb and feel dead”
- “I’m unsteady when I stand or walk”
- “I have open sores on my feet”
<table>
<thead>
<tr>
<th>What would a “perfect” exercise program look like?</th>
</tr>
</thead>
<tbody>
<tr>
<td>I have to be cautious of trips and falls while exercising</td>
</tr>
<tr>
<td>Hard to exercise due to being tired from all the meds to help with pain</td>
</tr>
<tr>
<td>I would love to exercise but I can barely walk.</td>
</tr>
<tr>
<td>I was told exercise wouldn’t help me.</td>
</tr>
<tr>
<td>Exercise helps me … just have to know the right exercise .. examples include yoga, water aerobics, walking, or bike if you can</td>
</tr>
<tr>
<td>It sucks not being able to play sports</td>
</tr>
<tr>
<td>Comment</td>
</tr>
<tr>
<td>------------------------------------------------------------------------</td>
</tr>
<tr>
<td>I fall more times than I can count</td>
</tr>
<tr>
<td>Not yet, but have come close</td>
</tr>
<tr>
<td>Fell in a freezing cold garage. Friend happened by and saved my life.</td>
</tr>
<tr>
<td>Scared the &amp;$*+ out of me</td>
</tr>
<tr>
<td>I fall, it hurts, but it hurts my pride the most</td>
</tr>
<tr>
<td>I fall maybe 10 times/year but I am VERY cautious</td>
</tr>
<tr>
<td>I trip and stagger a lot</td>
</tr>
</tbody>
</table>
Do you have fatigue due to your neuropathy?

I always feel fatigue.

I started using a pedometer and can increase my activity level without associated fatigue

My balance is always worse when I am tired, and I am always very tired after I exercise.

My feet hurt and it fatigues me too much

Exhausted with debilitating fatigue

After being on feet, spend a lot of time laying down, definitely unsteady.
What is the patient’s perspective?

Mixed methods study on fatigue in diabetes
(Singh, Kluding in preparation)

• Predictors of fatigue score (n=48):
  – Sleep quality / Pain / BMI
• Individual interviews (n=10):
  – Glucose fluctuations, depression
  – Impact of fatigue

Because I’m tired, sometimes I just don’t want to deal with people

sometimes it’s just having the energy to go take a shower and wash my hair

I haven’t done any housework in over a month

She (daughter) has to literally drag me out. I really don’t do anything.
International Classification of Functioning, Disability, and Health (ICF): World Health Organization
International Classification of Functioning, Disability, and Health (ICF): World Health Organization

Health Condition

Body Function / Structure

Environmental Factors

IENF, NCS, Pain, Fatigue

Activities

Balance

Walking

Personal Factors

Participation

QOL

Hyperglycemia, insulin resistance
Is Exercise Effective in DPN?
Focus on Pain

Single group trial, DPN (n=17), 10 weeks supervised aerobic/resistance exercise (Kluding et al 2012)

- Decrease pain on VAS (-1.8 on 10 point scale)

Single group trial, subjects with painful DPN (n=14): 16 weeks supervised aerobic exercise (Yoo, Sharma, LeMaster, Kluding in review)

- No change in pain intensity “due to your diabetes” (BPI-DPN)
- Significantly reduced pain interference (how has “pain with diabetes has interfered with your …”) in areas of walking, normal work, relationship with others, sleep
  - Average of 7 items -1.93 on 10 point scale
Is Exercise Effective in DPN?  
Focus on Fatigue

Single group trial, DPN (n=18), 16 weeks supervised aerobic exercise (Kluding et al 2015)

<table>
<thead>
<tr>
<th>MFI - 20</th>
<th>Pre-intervention mean (sd)</th>
<th>Post-intervention mean (sd)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>General fatigue</td>
<td>15.7 (2.3)</td>
<td>12.2 (4.2)</td>
<td>0.004*</td>
</tr>
<tr>
<td>Physical fatigue</td>
<td>15.5 (2.4)</td>
<td>12.4 (3.7)</td>
<td>0.003*</td>
</tr>
<tr>
<td>Mental fatigue</td>
<td>10.65 (3.6)</td>
<td>9.59 (3.7)</td>
<td>0.229</td>
</tr>
<tr>
<td>Reduced motivation</td>
<td>11 (3.7)</td>
<td>10.4 (3.2)</td>
<td>0.564</td>
</tr>
<tr>
<td>Reduced activity</td>
<td>14 (3.2)</td>
<td>11.8 (4.6)</td>
<td>0.078</td>
</tr>
</tbody>
</table>
Range of Outcomes: Evidence?

Pain

Falls

QOL

Fatigue
Thanks to …

Doug Wright, PhD
Mamatha Pasnoor, MD
Graduate Students:
  Rupali Singh, PhD
  Jason Rucker, PhD
  Steve Jernigan, PhD
  Linda D’Silva, PT (PhD student)
  Min Yoo, MSCR (Medical student)

Supported by a CTSA grant from NCATS awarded to the University of Kansas Medical Center for Frontiers: The Heartland Institute for Clinical and Translational Research # UL1TR000001; # TL1TR000120 (for MY), and #T32HD057850 (for LD).
Panel discussion:

Q&A, clinical application and future directions
References


References


References

LeMaster J, Mueller MJ, Reiber GE, Mehr DR, Madsen RW, Conn VS. Effect of Weight Bearing Activity on Foot Ulcer Incidence in People with Diabetic Peripheral Neuropathy: The Feet First Randomized Controlled Trial. *Physical Therapy*; 2008; 88:1385-1398; PMCID: PMC3637853


References


Tuttle LJ, Sinacore DR, Cade WT, Mueller MJ. Lower physical activity is associated with higher inter-muscular adipose tissue in people with type 2 diabetes and peripheral neuropathy. Physical Therapy 2011; 91:923-930. PMID: 21474636; PMCID: PMC3107439.

## Diabetic/Neuropathic Foot Screening

### Lower Extremity Exam: (Mark Y = Yes/Present or N = No/Absent)

<table>
<thead>
<tr>
<th></th>
<th>Right</th>
<th>Left</th>
<th>Right</th>
<th>Left</th>
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</thead>
<tbody>
<tr>
<td><strong>1. Neurologic Sensation (5.07 SW monofilament)</strong></td>
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<tr>
<td>Metatarsal Heads</td>
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<tr>
<td>Heel</td>
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</tr>
<tr>
<td>Medial Arch</td>
<td></td>
<td></td>
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<tr>
<td>Lateral Arch</td>
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<tr>
<td><strong>2. Tendon Jerks</strong></td>
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<tr>
<td>Knee Jerk</td>
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<tr>
<td>Ankle Jerk</td>
<td></td>
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<tr>
<td><strong>3. Muscle Strength: 5/5 = Yes &lt; 5/5 = No</strong></td>
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<tr>
<td>Tibialis Ant.</td>
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<tr>
<td>Gastroc/Soleus</td>
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<tr>
<td>Ext. Hallucis Longus</td>
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<tr>
<td><strong>4. Circulation</strong></td>
<td></td>
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<tr>
<td>Dorsalis Pedis</td>
<td></td>
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<tr>
<td>Capillary Refill (&lt;5 secs.)</td>
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<tr>
<td>Tibialis Posterior</td>
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<tr>
<td><strong>5. PROM</strong></td>
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<tr>
<td>Dorsiflexion (&gt; 10 deg.)</td>
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<tr>
<td>Great Toe Extension (&gt; 50 deg.)</td>
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<tr>
<td><strong>6. Nails</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Overgrown</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thickened</td>
<td></td>
<td></td>
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<tr>
<td>Missing</td>
<td></td>
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<tr>
<td>Discolored</td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>7. Skin: (Circle all that apply)</strong></td>
<td>Dry/Cool/Warm/Hair Loss/Discolored/Normal</td>
<td>Key: C = Callous</td>
<td></td>
<td></td>
</tr>
<tr>
<td>U= Ulcer</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B = Blister</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>R = Red Area</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>*<em>8. <em>Foot Deformities (Circle all that apply)</em></em></td>
<td>Hallux Valgus/Prominent MTH’s/Charcot/Hammer/Claw Toes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bunions/Equinous/Partial Amputation/Hallux Rigidus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>9. Footwear: (Circle)</strong></td>
<td>Type = Adequate/Inadequate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fit = Adequate/Inadequate</td>
<td>Describe Shoes________________________</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total _________</td>
<td></td>
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</table>

### Risk Category

<p>| | |</p>
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<thead>
<tr>
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</thead>
<tbody>
<tr>
<td><strong>Low</strong></td>
<td>≤ 2 Risk Factors</td>
</tr>
<tr>
<td><strong>Medium</strong></td>
<td>3-4 Risk Factors</td>
</tr>
<tr>
<td><strong>High</strong></td>
<td>≥ 5 Risk Factors or positive for * item</td>
</tr>
</tbody>
</table>

### General Health Screening:

**Blood Pressure:** ________/______ (normal <120/<80, BP >140/>90 requires MD attention)

**Most recent hemoglobin A1c:** ________ Date of test:__________ (ADA recommendation: <7%)

Combined Sections Meeting, American Physical Therapy Association, Indianapolis, IN 2015