Diagnostic criteria for peripheral neuropathy in metabolic syndrome

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Neuropathy in prediabetes/metabolic syndrome overall concepts:

- Metabolic syndrome represents a complex continuum of disorder and risk.
- Metabolic syndrome features contribute to the pathogenesis of neuropathy, and confer variable degrees of risk for neuropathy.
- Phenotypic diagnostic criteria for neuropathy in metabolic syndrome are the same as for DPN, but diagnostic certainty is comparatively reduced.
Why establish diagnostic criteria for prediabetic neuropathy?

Remarkably large risk pool; 35% of US population. Recognition of disease early in its course allows effective treatment.

To codify prediabetic neuropathy as disease entity:
- allows diagnostic consideration in general practice.
- Is foundational to examining the consequences of the disorder
- encourages further study of the pathogenic contributions of its component parts.

Helps to define neuropathy in the spectrum of metabolic syndrome disorders

Springboard for consideration of complex genetic risk factors
Clinical phenotype of hyperglycemic neuropathy

Distal polyneuropathy indistinguishable from that seen in diabetes

- Sensory first, predominant
- Distal, symmetrical
- Often painful
- Autonomic involvement
- ? Small fiber predominance

Essentially any feature of diabetic neuropathy can occur in the prediabetic setting
Nomenclature of the disorder

- “Prediabetic Neuropathy”
  - Ties to diabetes
  - Does not adequately recognize contribution of other features

- Impaired glucose tolerance neuropathy

- Cryptogenic Sensory Polyneuropathy (CSPN)

- Polyneuropathy in Metabolic Syndrome (PiMS)
Evidence for PiMS

- Epidemiology
  - Effect of MS features in diabetic neuropathy
  - Risk of MS features in otherwise idiopathic neuropathy
  - Risk of neuropathy in prediabetic MS

- Animal models recapitulate PiMS

- Treatment studies in prediabetic neuropathy

- Biological research on pathogenic effects of individual MS components, particularly obesity and dyslipidemia
Neuropathy associated with metabolic syndrome

Cutaneous Measures of Neuropathy in Diabetes

- 221 Subjects (48% female)
- 57 +/- 9 years old
- Diabetes duration 87 +/- 79 months.
- Hemoglobin A1c 6.8 +/- 1.5
- Body mass index 33.6 +/- 7.8.
- 17% no, 45% possible, 38% definite neuropathy

Smith, Singleton *J Diab Comp*, 2013
Obesity, hypertriglyceridemia and metabolic syndrome associated with increased neuropathy prevalence

Hypertension

Obesity

HDL

TRG

Metabolic Syndrome

Smith, Singleton *J Diab Comp*, 2013
Targeted metabolic syndrome therapy reduces diabetic complications in Steno 2

Neuropathy and neuropathic pain are more common in prediabetic patients than controls.

Ziegler et al. *Diabetes Care*, 2008
Neuropathy is associated with prediabetes

497 members of the Prospective Pancreatic Metabolism and Islet Cell Evaluation (PROMISE) cohort who had 3 year follow-up. Neuropathy symptoms based on MNSI of 2 (or 3) of 10 questions. Neuroesthesiometer use to measure vibration sensation threshold.

Lee, Perkins et al *Diabetes Care*, 2015
Neuropathy is associated with metabolic syndrome features

2382 Health ABC study participants
“Neuropathy” if + to 1 of 2 questions and had abnormality of PCV or 10g monofilament

1.1% increase in neuropathy for each MS component
Waist circumference and HDL associated with DSP secondary measures

Callaghan et al *Diabetes Care*, 2016
Proinflammatory, neurotoxic adipokines

An inflammatory disease:

- Enlargement
- Lipolysis
- FFAs
- "Adipokines"
- Cytokines
- Inflammatory mediators
- Macrophage invasion

Interleukin-6
Plasminogen activator inhibitor 1 (PAI-1)
TNF-α
Leptin
Angiotensinogen

Adiponectin
Neuropathy pathogenesis

- Insulin resistance
- ↑FFAs
- hyperglycemia
- ↑TNF-α/ceramide
- eNOS inhibition
- ROS detoxification
- NO
- endothelial injury
- reduced vascular reactivity
- direct nerve injury
- Obesity, dyslipidemia
- adipokines
- AGEs
- FA oxidation
- polyol pathway
- transition metals
- immune activation
Bariatric candidates are more likely to meet symptomatic and exam thresholds of neuropathy

Body mass index correlates with features of distal peripheral axonal injury
Rodent Models of Prediabetes

**Approaches:**
- Western diets (45% fat, high sucrose)
- High Fat diets (50—60% fat; lard)
- Standard American Diet (flour, sucrose)

**Metabolic Abnormalities**
- Increased body weight
- Mild hyperglycemia
- Increased serum insulin
- Impaired glucose tolerance
- Insulin resistance
- Increased cholesterol
Rodent Models of Prediabetes

Behavioral Abnormalities
- Mechanical allodynia
- Thermal hypersensitivity
- Cognition and memory deficits
- Chemogenic hypersensitivity

Neuropathy Changes
- Decreased SNCV (longterm)
- Decreased MNCV (longterm)
- Mild to no IENF changes
Rodent Models of Prediabetes

- Highly strain-, vendor-, and species-dependent
- Sensitive to fat and carbohydrate levels
- Pain behavior appears earlier than PNS pathology
- CNS and PNS likely impacted
- Strongly impacted by activity levels

![Graph showing Meters Traveled](image)

**C57BL/6-CR**

![Graph showing Withdrawal Threshold](image)

**C57Bl/6-J**

![Graph showing Withdrawal Threshold](image)
High fat diet produces DSP in B6wt mice...

..and dietary change reverses it

Hinder et al *Dis Mod Mech* 2017
### IGTN subject characteristics

Subjects: 71, 29 followed for up to three years

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>56</td>
<td>41-75</td>
</tr>
<tr>
<td>Body mass index</td>
<td>32.8</td>
<td>23-41.5</td>
</tr>
<tr>
<td>Reported minutes of exercise</td>
<td>15</td>
<td>0-120</td>
</tr>
<tr>
<td>Months of neuropathy</td>
<td>54</td>
<td>12-180</td>
</tr>
<tr>
<td>OGGT glucose (0/2h)</td>
<td>101/166</td>
<td>142-199 (2h)</td>
</tr>
</tbody>
</table>

Percent with:
- hypertension 86
- hyperlipidemia 81
- metabolic syndrome 73
- microalbuminuria 10
Sustained improvement in glucose and weight…

71 patients with IGT and neuropathy offered diet and exercise counseling based on the DPP, followed up to 3 years.

Smith, Singleton, *Diabetes Care*, 2006
Improved metabolic function results in significant improvement in intraepidermal nerve fiber density (IENFD)

Smith, Singleton, Diabetes Care, 2006
Capsaicin axotomy protocol applied to patients with prediabetes and metabolic syndrome

**Study Groups**
- Normal controls (20)
- Metab syndrome (24)
- Diabetes plus MS (30)

**Study measures**
- Consent/ screen
- Neuropathy measures
- Skin biopsy
- Metabolic measures
- Fitness testing
- MRI
- Adipokines/ oxidative stress

Reinn 1: diet, 2/week exercise
Reinn 2: community follow-up

Singleton et al *Ann Neurol*, 2015
Lifestyle intervention results in improved cutaneous nerve regenerative capacity

Singleton et al. *Ann Neurol*, 2015
Neuropathy in Metabolic Syndrome summary

Metabolic syndrome represents a complex continuum of disorder and risk. Metabolic syndrome features contribute to the pathogenesis of neuropathy, and confer variable degrees of risk for neuropathy. Phenotypic diagnostic criteria are the same as for DPN, but diagnostic certainty is comparatively reduced.
Diagnostic criteria for PiMS

No authoritative diagnostic criteria have been established

*Recommended:*
Symptoms and exam findings of neuropathy + confirmatory testing as promulgated for diabetic neuropathy
Presence of metabolic syndrome by ATPIII criteria
Features not better ascribed to another neuropathic disorder
Recognition that neuropathy etiology may be multifactorial
## Competing metabolic syndrome diagnostic criteria

### WHO definition (fasting hyperinsulinemia or impaired glucose regulation plus > 2 more factors)

- Also (a) fasting insulin in the upper quartile in non-diabetic or
- (b) fasting blood glucose ≥ 110 mg/dL plus ≥ 2 of the following:
  - Systolic blood pressure ≥ 140/ and/or diastolic ≥ 90 mmHg
  - Dyslipidemia: triglyceride ≥ 150 mg/dL or HDL < 35 in men or < 39 m/dL in women
  - Central obesity, waist-to-hip ratio > 0.90 in men or > 0.85 in women and/or BMI > 30 kg/m2
  - Microalbuminuria (≥ 20 μg/min or albumine/creatinine ≥ 30 mg/g)

### ATPIII definition (≥ 3 of 5 risk factors)

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Criteria</th>
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<tbody>
<tr>
<td><strong>Waist circumference</strong></td>
<td></td>
</tr>
<tr>
<td>102 cm in men</td>
<td></td>
</tr>
<tr>
<td>88 cm in women</td>
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<tr>
<td><strong>Blood pressure</strong></td>
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<tr>
<td>≥ 130 mmHg systolic and/or</td>
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<tr>
<td>≥ 85 mmHg diastolic</td>
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<tr>
<td><strong>Plasma glucose</strong></td>
<td></td>
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<tr>
<td>≥ 110 mg/dL</td>
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<tr>
<td><strong>Triglyceride</strong></td>
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<tr>
<td>150 mg/dL</td>
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<tr>
<td><strong>HDL-cholesterol</strong></td>
<td></td>
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<tr>
<td>&lt; 40 mg/dL in men</td>
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<tr>
<td>&lt; 50 mg/dL in women</td>
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### Table 1 - Clinical criteria defining metabolic syndrome

Diagnostic criteria for PiMS

Questions/ controversies
• Should small fiber involvement be emphasized?
• Should some MS criteria be given greater diagnostic weight?
• Can PiMS be present with partial fulfillment of MS?
• Establish “early” vs. “advanced” neuropathy criteria?
• Which specific MS criteria (e.g. ATP III) are most appropriate, responsive?
• Does a considered diagnosis of PiMS mandate more intensive evaluation for other causes of neuropathy than does diabetes?
• Need for genetic analysis to identify genetic features associated with increased risk for early hyperglycemic/MS associated neuropathy.
Metabolic syndrome is more prevalent among both IGT and NGT patients with neuropathy.

- 238 sequential idiopathic neuropathy patients seen between 1997-2003 who underwent an OGTT.
- Hereditary and inflammatory neuropathy excluded.
- Other common causes of neuropathy excluded (B12, TSH, SPEP/IFIX, ANA).

Smith AG, Rose K, Singleton JR. J Neuro Sci. 2008