Best Practices in Cardiometabolic Disease Management after SCI: Should We Transcend the Guidelines?

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Disclosures

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At the conclusion of this activity, the participant will be able to:

A. Identify two component risks for Cardiometabolic Syndrome as a health risk for persons aging with SCI
B. Name two guideline-driven interventional approaches on Cardiometabolic Syndrome.
C. Name one drug that has been shown effective for treating lipid disorders in persons with SCI
Cardiometabolic Disease: NOT just your everyday bland fat storage disorder

Hyperglycemia
Impaired Glucose Tolerance
Impaired Fasting Glucose

Hyperinsulinemia
Visceral Obesity
Dyslipidemia

Hypertension

Pro-Inflammatory
↑ CRP / IL-6

Insulin Resistance
Cardiovascular Disease

Obesity

Clustering of Health Risks

Pro-thrombotic

+/- T2DM

IR & CVD

Endothelial Dysfunction

Visceral Obesity
Dyslipidemia

Hyperinsulinemia
Consequences of ill-health extend beyond ‘health conditions’

“health…a resource for everyday life, not the object of living.”

WHO Ottawa Charter for Health Promotion, 1986

A health-centered life will be - as best possible… active, satisfying, and productive.

Key Factors in Cardiometabolic Disease that Require Extra Diligence for Persons with SCI

- The typical diet is hypercaloric and excessive in calories from saturated fats.
- Poor fitness is a contributor to both CVD and functional decline.
- The population is aging, or injured at an older age, which worsens health prognosis.
Evidence Report/Technology Assessment
Number 163

Carbohydrate and Lipid Disorders and Relevant Considerations in Persons with Spinal Cord Injury

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...the existing evidence does not indicate that adults with SCI are at markedly greater risk for carbohydrate and lipid disorders or subsequent cardiovascular sequelae than able-bodied adults.

Cardiovascular diseases are among the leading causes of death in aging patients with chronic SCI.

..., patients with SCI should be assessed and treated according to existing guidelines for able-bodied individuals to reduce cardiac morbidity and mortality in this population associated with carbohydrate and lipid disorders.
Arguments for Cardiometabolic Primary Prevention after SCI

• Little credible evidence even remotely suggests that SCI, its unique physiology, or $2^0$ complications are cardioprotective.

• CVD progression is largely silent, and we can only speculate as to who is in jeopardy of developing CVD unless: (1) their risk is systematically assessed, (2) a life-threatening cardiac event occurs, or (3) sudden death ensues.

• An enlightened and compassionate health care system – and a caring society – will favor early assessment and aggressive treatment over unknown risks of frank morbidity and uncertain mortality.
Arguments for Cardiometabolic Primary Prevention after SCI

- Early risk assessment, quick symptom recognition, and rapid interventional care, are less likely to occur for persons with SCI.

- CVD-associated cardiocirculatory deficits and residual secondary impairments in persons with SCI will render more challenging every aspect of daily activity, productivity, health, and independence.

- The notion that the SCI population is at no greater risk that those without SCI ought afford little comfort… PREVALENCE ≠ RISK
National Cholesterol Education Project Adult Treatment Panel III Guidelines: A Four-step Sequential Algorithm for the Management of Dyslipidemia and CVD

1. Eliminate Drugs and Biologicals that worsen the lipid/glycemic profile
2. Undertake Dietary Modification
3. Incorporate Exercise
4. Pharmacological Intervention

Candidate Drugs and Biologicals that Worsen Cardiometabolic Risks

- Tobacco
- Corticosteroids
- Receptor-selective adrenergic antagonists
  - ‘Beta-blockers’
- Thiazide Diuretics
- Antipsychotics
  - Zyprexa (Olanzapine)
  - Clozaril (Clozapine)

- Double-Inhibitor Antidepressants (SSNRI’s)
  - Cymbalta (Duloxetine)

Neuropathic pain?
What is known about effects of SCI on dietary habits?

- Excessive in calories and saturated fat
- Worsened by lower metabolic rates associated with injuries above T1 (i.e., functional sympathectomy)
- Overfeeding begins in rehabilitation from injury and often becomes habit
- Imprudent diet is not offset by exercise activity
  - Combination strategies of exercise and diet are needed for weight management

~ 875 kcal/day

Exercise After SCI


Pharmacotherapies

**Lipid Metabolism Disorders**
- Bile Acid Sequestrates
- Fibric Acid Derivatives
- Cholesterol Uptake Blockers
- HMG-CoA Reductase Inhibitors (Statins)
- Extended-Release Niacin

**Glycemia Metabolism Disorders**
- $\alpha$ – Glucosidase Inhibitors
- Sulfonylureas
- Biguanides
- Thiazolidinediones (TZDs)
- Incretins
  - GLP-1 Agonists
  - DPP-IV Inhibitor
Drug Therapy Options: Advantages and Disadvantages of Niacin ER (Niaspan™)

- FDA Approved
- Long-recognized as the first-line drug for elevating low HDL-C (~26% at 2g QHS)
- Lowers TC, LDL-C, and TG by ~17-35%
- 26% reduction in recurrent nonfatal MI, 11% reduction in total mortality.

- Adverse Events (at 2g QHS)
  - Flushing (88% trial prevalence)*
  - Hepatotoxicity (1% at 3x ULN)
  - HA (8% vs. 15% placebo)
  - GI (8% vs. 8% placebo)
  - Hyperuricemia
  - Glucose Elevation (~5 mg/dL)
- Requires pretreatment with ASA 325g


*6% discontinuation
Study Description

- **Randomized, Blinded, Placebo-controlled, Dose-escalation Clinical Trial at Three NIDRR-designated Model SCI Centers**
- **Quasi-Phase I/II Study: Safety, Tolerance, And Efficacy**
  - Clinical Endpoint: Full Niacin ER Dose Escalation (500 mg to 2 g QHS over 4 months)
  - 32 Week Post-escalation Extension Phase
  - ‘Intention-to-treat’ clinical trial standards
- **Participants**
  - 54 Healthy Non-smoking Persons with Chronic (> 1 year) Tetraplegia
  - Ages 18-65
  - HDL < 40 mg/dL, TC < 240 mg/dL, TG< 250 mg/dL
  - Not on lipid or glucose lowering agents
  - Instructed to maintain habitual diet
## Data Collected & Participant Responses Recorded

<table>
<thead>
<tr>
<th>Dose Escalation (g QHS)</th>
<th>Baseline</th>
<th>Week 4</th>
<th>Week 8</th>
<th>Week 12</th>
<th>Week 16</th>
<th>Week 20</th>
<th>Week 24</th>
<th>Week 48</th>
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</table>

### Safety: SAE’s and AE’s
- ALT, AST, ALP, Bili, UA, FBG

<table>
<thead>
<tr>
<th>Safety: HbA1c</th>
<th>Baseline</th>
<th>Week 4</th>
<th>Week 8</th>
<th>Week 12</th>
<th>Week 16</th>
<th>Week 20</th>
<th>Week 24</th>
<th>Week 48</th>
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</tbody>
</table>

### Tolerance: (Frequency/Intensity)
- Insomnia, flushing, HA, myalgia, arthralgia, dyspepsia, pruritis, open-ended

<table>
<thead>
<tr>
<th>Tolerance: HbA1c</th>
<th>Baseline</th>
<th>Week 4</th>
<th>Week 8</th>
<th>Week 12</th>
<th>Week 16</th>
<th>Week 20</th>
<th>Week 24</th>
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</tbody>
</table>

### Effectiveness: HDL-C, LDL-C, TC, TG
- TC:HDL ratio, LDL:HDL ratio

<table>
<thead>
<tr>
<th>Effectiveness: HDL-C, LDL-C, TC, TG</th>
<th>Baseline</th>
<th>Week 4</th>
<th>Week 8</th>
<th>Week 12</th>
<th>Week 16</th>
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</table>
## Study Withdrawals for Treatment and Non-Treatment Related Events; 10,243 Drug Dosings, 7482 @ 2 grams

<table>
<thead>
<tr>
<th>N</th>
<th>Study Arm</th>
<th>Cause for Withdrawal</th>
<th>Study Week</th>
<th>IRB / DSMB Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>ER-N</td>
<td>Loose Stool / Diarrhea</td>
<td>4</td>
<td>Probably Related (AE)</td>
</tr>
<tr>
<td>1</td>
<td>Placebo</td>
<td>Fracture</td>
<td>36</td>
<td>Unrelated</td>
</tr>
<tr>
<td>1</td>
<td>ER-N</td>
<td>Flushing</td>
<td>4</td>
<td>Related (AE)</td>
</tr>
<tr>
<td>1</td>
<td>ER-N</td>
<td>Flushing / Transient Hypotension</td>
<td>1</td>
<td>Related (SAE)</td>
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<tr>
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<td>ER-N</td>
<td>Pre-Syncope/Hypotension</td>
<td>24</td>
<td>Probably unrelated</td>
</tr>
<tr>
<td>1</td>
<td>ER-N</td>
<td>Pressure Ulcer</td>
<td>8</td>
<td>Unrelated</td>
</tr>
<tr>
<td>1</td>
<td>ER-N</td>
<td>Requested Group Reassignment, Denied</td>
<td>16</td>
<td>Unrelated</td>
</tr>
<tr>
<td>6</td>
<td>5 Placebo 1 ER-N</td>
<td>Transportation / Relocation / Logistics</td>
<td>4-48</td>
<td>Unrelated</td>
</tr>
<tr>
<td>14</td>
<td>8 ER-N, 6 Placebo</td>
<td></td>
<td></td>
<td>4/14 Related / Probably Related</td>
</tr>
</tbody>
</table>
Effects of ER-N and Placebo on UA, Hepatic Transaminases, Alkaline Phosphatase, and Total Bilirubin
Effects of ER-N and Placebo on Fasting Glycemia and Hemoglobin A1c

- **Fasting Blood Glucose (mg/dL):**
  - **Baseline:**
  - **24 Weeks:**
  - **48 weeks:**

- **Glycated Hemoglobin (HbA1c %):**
  - **Baseline:**
  - **24 Weeks:**
  - **48 weeks:**

- **Graphs:**
  - **Fasting Blood Glucose:**
    - ER-N
    - Placebo
  - **Glycated Hemoglobin:**
    - ER-N
    - Placebo
Flushling and Insomnia: Frequency and Intensity

**Flushing Frequency Likert Score (Niaspan)**

- Percentage of respondents rating frequency of flushing symptoms.
- Escalation.
- I Drop.
- No dose-dependency.

**Insomnia Frequency Likert Score (Niaspan)**

- Percentage of respondents rating frequency of insomnia symptoms.
- Escalation.
- ns group, time, or group x time effects. No dose-dependency.

**Flushing Intensity (0-100)**

- p< 0.05 for group and time.
- Escalation.

**Insomnia Intensity (0-100)**

- ns group, time, or group x time effects. No dose-dependency.
Effects of ER-N and Placebo on Lipids, Lipoprotein Cholesterols, and Global Risk Ratios:

- p’s < 0.05 for group, time, and group x time interaction
- no interaction effect for TC
Dose-dependent Responses of ER-N on HDL, LDL-C, and TC

* p< 0.05, dose main effect and all doses different from one other
Summary Findings

• Safe (~10K dosings)
  • 1 SAE, 3 AE, 12.9% event rate: about ½ of clinical trials involving persons without disability
  • No hepatotoxicity, hyperuricemia, or dysglycemia

• Tolerated
  • 3% flushing dropout rate: about ½ of clinical trials involving persons without disability
  • Minor effects on discomfort, and no relationship to sleep or other symptoms of myalgia, arthralgia, pruritus, etc.

• Effective
  • Corrected low HDL
  • Lowered LDL-C, TG, and TC
  • Corrected elevated global risks from elevated TC:HDL and LDL:HDL
Novel Study Observations

• 1 subject withdrew after two months because he wanted to be in the drug arm, but – in fact - he was. ("The power of placebo!").

• 6 subjects – all drug randomized - reported enjoying the feeling of body warmth for the first time since their SCI. Mostly a New Jersey ‘winter-thing’.

• Some subjects reached lipid targets at less than full dose.
Special Precautions and Recommendations

- **Hypotension**
  - Administer first dose at each titration level where BP can be monitored.

- **Loose Stools**
  - May require adjustment of stool softeners.

- **Flushing**
  - Varying degrees and tolerance for cutaneous flushing. Assess on a case basis.
The Best Practice Puzzle of Cardiometabolic Disease

Nash et al. DoD-funded RCT on Obesity and Cardiometabolic Syndrome after SCI.


PVA: Clinical Practice Guidelines for Carbohydrate and Lipid Metabolism: Associated Cardiovascular Risk in Persons with Spinal Cord Injury


NIDRR KT Center: Groah, S.L, and M.S. Nash. A systematic review of cardiometabolic risks after SCI.


The Multidimensional Challenges of Spinal Cord Injury

- Health
- Growth Factors
- Re-myelination
- Neural Bridges
- Axonal Regeneration
- Function
- Transplant Strategies
- Inhibitory Factors
- Rehabilitation

- Evidence of Risk
- Dietary Therapy
- Exercise Therapy
- Pharmacotherapy
• Cardiometabolic disease and all-cause CVD remain a serious concern for the SCI community made more compelling by population aging.

• Medicine of the highest order requires adoption of guideline-driven assessment and therapy if best health, function, and longevity are to be preserved.

• We are even less prepared to rehabilitate cardiometabolic disease in those with SCI than prevent it, making primary prevention a lifestyle and medical strategy that oblige widespread adoption.

• Transcend the Guidelines…
Colleagues…

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and Debbie Backus, Ph.D., PT
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• This information can also be found in the Summit 2011 Program on page 8.