Is Risk for Diabetes Associated with Disrupted Descending Modulation of Pain and Spinal Nociception?

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**Introduction**

Disruption of glucose and insulin metabolism can affect small diameterafferents, which can occur early in the progression of diabetes. This is believed to be one of the mechanisms promoting diabetic neuropathy. However, robust studies have implicated a central mechanism in diabetic neuropathy, possibly a disruption of descending modulation. Indeed, human evidence indicates painful diabetic neuropathy is associated with disrupted exercise-induced inhibition. The present study examined whether conditioned pain modulation (CPM; a measure of central pain inhibition in which pain inhibits pain) was associated with diabetes risk in 179 participants without a current diagnosis of diabetes.

**Objective**

To determine whether diabetes risk is associated with disrupted conditioned pain modulation, a measure of central pain inhibition.

**Participants**

- Healthy Participants: N = 179
- Female (49.2%), White, non-Hispanic (47.5%), age = 29.06 years (SD = 12.04), completed partial college (48.6%)
- Exclusion Criteria: <18 years of age, cardiovascular, neurological, dermatological problems, chronic pain condition, substance abuse, psychiatric symptoms, uncorrected visual problems, numbness, high blood pressure, diabetes, characterized by amplified spinal nociception and a reduced capacity to inhibit pain. As such, these groups were evaluated separately.
- CPM was among the last experimental procedures assessed during the testing day.

**Procedure**

- Participants provided consent after study procedures were explained.
- Participants completed background information for diabetes risk.
- Electric stimulus intensity individually calibrated for each participant to ensure a comfortable yet painful response.
- Sensors applied to all participants.
- EMG sensors
  - Biceps
  - Over sural
  - Femoris
- Participants received 5 painful electric stimulations while their hand was in cold water for 2 min. Participants completed a battery of pain tests after removing hand from water.

**Methods: Conditioned Pain Modulation (CPM)**

- CPM was among the last experimental procedures assessed during on the testing day.
- Sample size (Total N = 179)
- For CPM, 5 painful electric stimulations were received while their hand was in cold water for 2 min.
- The group with ≥3 risks showed no pain inhibition.
- The group with 0 risks showed significant NFR facilitation (p < .03).
- The group with ≥3 risks showed significant NFR facilitation (p < .01).
- The group with ≥3 risks showed significant NFR inhibition (p < .01).

**Results**

Diabetes risk influenced CPM of pain (p < .01).

- Groups with 0, 1, or 2 risks showed significant pain inhibition (p < .001).
- The group with ≥3 risks showed no pain inhibition.

**Data Analysis**

- Linear Mixed Model ANOVAs were conducted with Risk Factor Group and CPM phase (Pretest vs. Conditioning vs. Posttest) as IVs.
- Outliers were detected and replaced with nearest non-outlier neighbor value using WinpG's MAD-Median procedure.
- Significant group × Conditioning Phase interactions were followed up with Fisher’s LSD comparisons between Pretest and Conditioning phases.
- Graphs depict the difference in pain/NFR between Pretest and Conditioning (conditioning minus pretest).

**Conclusion**

These findings imply that central modulatory mechanisms may be altered in persons at highest risk for diabetes, characterized by amplified spinal nociception and a reduced capacity to inhibit pain. As such, these groups may benefit from interventions to improve pain modulation.

**Funding Source**

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**Research**

Disruption of glucose and insulin metabolism can affect small diameter afferents, which can occur early in the progression of diabetes. This is believed to be one of the mechanisms promoting diabetic neuropathy. However, robust studies have implicated a central mechanism in diabetic neuropathy, possibly a disruption of descending modulation. Indeed, human evidence indicates painful diabetic neuropathy is associated with disrupted exercise-induced inhibition. The present study examined whether conditioned pain modulation (CPM; a measure of central pain inhibition in which pain inhibits pain) was associated with diabetes risk in 179 participants without a current diagnosis of diabetes.

**Diabetes Risk**

- Several potential risk factors identified from the literature were assessed:
  - Age, Body Mass Index (BMI), current smoking habits, first degree relative with cardiovascular disease, first degree relative with diabetes, physical inactivity (IPAQ).
- The IPAQ was used to assess activity level. This measure places individuals into high categories of physical activities based on the amount of Metabolic Equivalent of Task.

**Diabetes Risk Factors**

1. Older age (years of age > 55)
2. Higher body mass index (BMI≥25)
3. Current Smoker
4. Low physical activity (IPAQ = low)
5. Family history of cardiovascular problems (self-report)
6. Family history of diabetes (self-report)

**Cumulative Risk**

- Total number of risk factors
- Participants were placed into groups based on their cumulative risk:
  - Group 0: risks, 1 risk, 2 risks, 3 risks

**CHARACTERISTICS**

<table>
<thead>
<tr>
<th>Risk</th>
<th>N = 68</th>
<th>N = 61</th>
<th>N = 27</th>
<th>N = 13</th>
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<tbody>
<tr>
<td>Sample Size (Total N = 179)</td>
<td>N=68</td>
<td>N=61</td>
<td>N=27</td>
<td>N=13</td>
</tr>
<tr>
<td>Female (%)</td>
<td>58.8%</td>
<td>58.0%</td>
<td>59.6%</td>
<td>76.9%</td>
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<td>Age (mean yrs, SD)</td>
<td>22.9 (3.9)</td>
<td>23.1 (3.7)</td>
<td>27.7 (3.6)</td>
<td>30.9 (4.4)</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>22.0 (4.8)</td>
<td>25.7 (7.4)</td>
<td>27.8 (3.6)</td>
<td>30.4 (8.4)</td>
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<tr>
<td>FH diabetes (n, %)</td>
<td>0</td>
<td>1</td>
<td>7</td>
<td>12</td>
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<tr>
<td>FH cardiovascular (n, %)</td>
<td>0</td>
<td>1</td>
<td>7</td>
<td>12</td>
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<td>Physical activity</td>
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<td>1 (2%)</td>
<td>7 (16%)</td>
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<td>NFR diabetes (n, %)</td>
<td>0</td>
<td>4 (6%)</td>
<td>14 (28%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

**NFR Magnitude**

- Conditioning: participants received 5 painful electric stimulations while their hand was in cold water for 2 min.
- Pretest: participants received 5 painful electric stimulations after removing hand from water.
- Posttest: participants received 5 painful electric stimulations after removing hand from water.

**Methods**

- CPM of pain (p < .01)
- Groups with 0, 1, or 2 risks showed significant pain inhibition (p < .001).
- The group with ≥3 risks showed no pain inhibition.

**Conclusion**

- These findings imply that central modulatory mechanisms may be altered in persons at highest risk for diabetes, characterized by amplified spinal nociception and a reduced capacity to inhibit pain. As such, these groups may benefit from interventions to improve pain modulation.

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