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Association of metabolic syndrome and change in Unified Parkinson's Disease Rating Scale scores.

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Association of metabolic syndrome and change in Unified Parkinson’s Disease Rating Scale scores

ABSTRACT

Objective: To explore the association between metabolic syndrome and the Unified Parkinson’s Disease Rating Scale (UPDRS) scores and, secondarily, the Symbol Digit Modalities Test (SDMT).

Methods: This is a secondary analysis of data from 1,022 of 1,741 participants of the National Institute of Neurological Disorders and Stroke Exploratory Clinical Trials in Parkinson Disease Long-Term Study 1, a randomized, placebo-controlled trial of creatine. Participants were categorized as having or not having metabolic syndrome on the basis of modified criteria from the National Cholesterol Education Program Adult Treatment Panel III. Those who had the same metabolic syndrome status at consecutive annual visits were included. The change in UPDRS and SDMT scores from randomization to 3 years was compared in participants with and without metabolic syndrome.

Results: Participants with metabolic syndrome (n = 396) compared to those without (n = 626) were older (mean [SD] 63.9 [8.1] vs 59.9 [9.4] years; p < 0.0001), were more likely to be male (75.3% vs 57.0%; p < 0.0001), and had a higher mean uric acid level (men 5.7 [1.3] vs 5.3 [1.1] mg/dL, women 4.9 [1.3] vs 3.9 [0.9] mg/dL, p < 0.0001). Participants with metabolic syndrome experienced an additional 0.6- (0.2) unit annual increase in total UPDRS (p = 0.02) and 0.5- (0.2) unit increase in motor UPDRS (p = 0.01) scores compared with participants without metabolic syndrome. There was no difference in the change in SDMT scores.

Conclusions: Persons with Parkinson disease meeting modified criteria for metabolic syndrome experienced a greater increase in total UPDRS scores over time, mainly as a result of increases in motor scores, compared to those who did not. Further studies are needed to confirm this finding.

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GLOSSARY

ATP III = Adult Treatment Panel III; BMI = body mass index; NCEP = National Cholesterol Education Program; NET-PD LS 1 = National Institute of Neurological Disorders and Stroke Exploratory Trials in PD Long-Term Study 1; PD = Parkinson disease; SDMT = Symbol Digit Modalities Test; UPDRS = Unified Parkinson’s Disease Rating Scale.

Metabolic syndrome is a combination of conditions—hypertension, hyperglycemia, hyperlipidemia, and increased waist circumference—that, when occurring together, escalate a person’s risk for heart disease, stroke, and diabetes mellitus. Recent studies suggest that the syndrome is also associated with increased risk of other diseases, including Parkinson disease (PD). However, studies on the association of metabolic syndrome or its components, e.g., hyperglycemia or diabetes mellitus, and PD have yielded inconsistent results. For example, recent meta-analyses of the association of diabetes mellitus and the risk of developing PD had
opposite conclusions: one that diabetes mellitus increases the risk of PD21 and another that it does not.22 Higher body mass index (BMI) in midlife, i.e., >25 kg/m², has been associated with an increased risk of PD in multiple studies16,18,23 but not in others.19,24 A recent study found that patients with PD with increasing BMI had slower PD progression than those with a stable or declining BMI25 as measured by the Unified Parkinson’s Disease Rating Scale (UPDRS). Another study reported that diabetes mellitus was associated with more rigidity and a parkinsonian-type gait in aging persons without a diagnosis of PD or dementia.26

To the best of our knowledge, the effect of metabolic syndrome on PD progression has not previously been studied. The aim of this study was to investigate the relationship between metabolic syndrome and progression of PD using change in UPDRS. Because metabolic syndrome may have a role in driving cognitive impairment in PD, we also explored the association of metabolic syndrome and a cognitive measure. Using data from the National Institute of Neurological Disorders and Stroke Exploratory Trials in PD Long-Term Study 1 (NET-PD LS 1),27 we compared the progression of PD in those who had metabolic syndrome throughout the first 3 years of the trial to those who were without evidence of metabolic syndrome.

**METHODS**

**Participants.** NET-PD LS 1 was a large, multi-center, placebo-controlled, randomized, double-blind trial of 10 mg creatine monohydrate vs placebo and was conducted from March 2007 to September 2013. The study was terminated early, 10 mg creatine monohydrate vs placebo and was conducted from March 2007 to September 2013. The study was terminated early.

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RESULTS Table 1 shows the demographic characteristics of the participants according to whether participants were categorized as having metabolic syndrome. Baseline mean age and mean uric acid levels were significantly different in these 2 groups, as well as the proportion of men and women in these 2 groups. Participants with metabolic syndrome were more likely to be men, to be older, and to have a higher mean uric acid level compared to those without metabolic syndrome.

Table 2 shows the change in total UPDRS over 3 years compared between the metabolic syndrome and no metabolic syndrome groups. On average, participants without metabolic syndrome experienced a 1.7-unit annual increase in total UPDRS score from their baseline values, while participants with metabolic syndrome experienced a 2.3- (1.7 + 0.6) unit annual increase in total UPDRS change from baseline after controlling for covariates. This information is also presented in the figure, which demonstrates that participants with metabolic syndrome were more likely to have increases in total UPDRS scores, especially in the third year of study.

Table 3 shows the change in motor UPDRS (part III) score, the secondary outcome measure, over 3 years compared between the 2 groups. On average, participants without metabolic syndrome experienced a 0.8-unit annual increase in their motor UPDRS score, while participants with metabolic syndrome experienced a 1.3- (0.8 + 0.5) unit increase per year.

DISCUSSION This study shows that participants with early-stage, treated PD who met modified criteria for metabolic syndrome had more rapid progression as measured by both the total and motor UPDRS scores, with participants with metabolic syndrome experiencing a 1.3- (0.8 + 0.5) unit increase per year. We could find no other study predictors of baseline SDMT, metabolic syndrome status, time in years, and the interaction term of metabolic syndrome and time in years, was adjusted for confounding variables of baseline age, total UPDRS score, sex, handedness, race, uric acid levels, and disease duration.

All statistical analyses were conducted with SAS statistical software (version 9.4, SAS Institute Inc, Cary, NC).

**Sensitivity analyses.** We considered alternative ways of analyzing the current dataset. We looked at the entire NET-PD LS1 cohort, dividing the metabolic vs no metabolic syndrome groups according to their status at baseline, and followed them for their entire participation in the study, up to 5 years, without regard to whether they changed status at any annual visit. We also ran the analyses with a stricter definition of metabolic syndrome, defining metabolic syndrome as having 3 or more of the 4 criteria rather than 2 or more as in the presented data. Furthermore, we ran the analyses with different criteria for metabolic syndrome, considering that if participants were taking an antihypertensive, anti-hyperlipidemia, or antihyperglycemic medication, they would not meet that criterion for metabolic syndrome because the indication was adequately treated. Each of these sensitivity analyses produced the same results. Because the results were the same as those presented here, they are not shown, but they are available on request from the authors.

Table 1 Baseline characteristics of participants (n = 1,022) by metabolic syndrome status

<table>
<thead>
<tr>
<th>Demographics</th>
<th>No metabolic syndrome (n = 626), mean (SD)</th>
<th>Metabolic syndrome (n = 396), mean (SD)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>59.9 (9.4)</td>
<td>63.9 (8.1)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>357 (57.0)</td>
<td>298 (75.3)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Disease duration, y</td>
<td>1.6 (1.1)</td>
<td>1.6 (1.1)</td>
<td>0.92</td>
</tr>
<tr>
<td>Total UPDRS score</td>
<td>25.0 (10.7)</td>
<td>26.0 (10.7)</td>
<td>0.16</td>
</tr>
<tr>
<td>Motor UPDRS score</td>
<td>17.0 (7.9)</td>
<td>17.7 (7.9)</td>
<td>0.14</td>
</tr>
<tr>
<td>Treatment with creatine, n (%)</td>
<td>310 (49.5)</td>
<td>188 (47.5)</td>
<td>0.52</td>
</tr>
<tr>
<td>Handedness: right, n (%)</td>
<td>560 (89.5)</td>
<td>352 (88.9)</td>
<td>0.78</td>
</tr>
<tr>
<td>Handedness: left/mixed, n (%)</td>
<td>66 (10.5)</td>
<td>44 (11.1)</td>
<td>0.78</td>
</tr>
<tr>
<td>White race, n (%)</td>
<td>586 (93.6)</td>
<td>365 (92.2)</td>
<td>0.38</td>
</tr>
<tr>
<td>Uric acid, men, mg/dL</td>
<td>5.3 (1.1)</td>
<td>5.7 (1.3)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Uric acid, women, mg/dL</td>
<td>3.9 (0.9)</td>
<td>4.9 (1.3)</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

Abbreviation: UPDRS = Unified Parkinson’s Disease Rating Scale.

Table 2 Change in total UPDRS

<table>
<thead>
<tr>
<th>Effects</th>
<th>Estimate (SE)</th>
<th>95% CI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic syndrome*</td>
<td>-0.6 (0.5)</td>
<td>-1.6 to 0.5</td>
<td>0.30</td>
</tr>
<tr>
<td>Time, y</td>
<td>1.7 (0.2)</td>
<td>1.4 to 2.0</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Metabolic syndrome × time</td>
<td>0.6 (0.2)</td>
<td>0.1 to 1.0</td>
<td>0.02</td>
</tr>
<tr>
<td>Uric acid, mg/dL</td>
<td>0.2 (0.2)</td>
<td>-0.1 to 0.5</td>
<td>0.29</td>
</tr>
</tbody>
</table>

Abbreviations: CI = confidence interval; SE = standard error; UPDRS = Unified Parkinson’s Disease Rating Scale.

*Metabolic syndrome is a dichotomized variable. In the model, the reference group is participants without metabolic syndrome. The site and treatment assignment (creatine vs placebo) were included as covariates.
showing an association between metabolic syndrome and progression of PD, so this finding needs confirmation. If confirmed, this would raise the possibility that improved treatment of metabolic syndrome could offer a novel approach to slowing PD progression.

How metabolic syndrome might accelerate PD progression is not known. Because metabolic syndrome is a combination of conditions, each of these conditions could contribute to the association. A recent analysis of the NET-PD population found that an increase in BMI was associated with a slower increase in UPDRS scores, so it seems unlikely that the high BMI component of metabolic syndrome contributes strongly to the association of metabolic syndrome and increasing UPDRS scores. Another metabolic syndrome condition, hypertension, could drive faster PD progression if it caused those affected to have more CNS ischemia or strokes. Brain imaging data were not collected in the NET-PD study, so this theory cannot be substantiated with our data. Regarding blood triglyceride, glucose, and high-density lipoprotein cholesterol levels, the literature to date is conflicting, lacking, or not informative. Insulin resistance and inflammation underlie metabolic syndrome, and these pathologic mechanisms also contribute to the progressive loss of dopaminergic cells that results in PD. The association found between metabolic syndrome and PD may therefore be attributed to common pathophysiologic pathways.

The faster progression of motor signs in our participants with metabolic syndrome compared to those without could be related to the accumulating evidence of brain abnormalities in the expression of insulin and insulin growth factors and their related receptors and CNS insulin resistance being reported in PD. Activities of insulin growth factors include support of neuronal growth and survival. Recent literature suggests that these insulin-related CNS abnormalities may increase sensitivity to neurotoxins and the accumulation of α-synuclein. While further studies are needed to judge whether these brain abnormalities correlate with clinical longitudinal signs, given that patients with PD have CNS insulin-related abnormalities that normally play a protective role, concurrent metabolic syndrome is likely to exacerbate these baseline abnormalities and to enhance the progression of disease.

While uric acid levels are not a defined component of metabolic syndrome, the syndrome is associated with higher uric acid levels. Studies to date suggest that higher uric acid levels are associated with more slowly increasing UPDRS scores. In this study, however, the metabolic syndrome group had higher uric acid levels and had faster increasing UPDRS scores.

The association of metabolic syndrome and cognitive function was explored in this study. In NET-PD, the only cognitive measure captured at annual visits was the SDMT score. There was no significant difference: 0.3- vs 0.2-unit annual decline in participants with metabolic syndrome vs without (p = 0.77).

However, this analysis was limited by the minimal decline in SDMT scores that occurred in this early treated PD group. Furthermore, the SDMT evaluates attention and not other cognitive domains or global cognitive function.

A strength of this study is that it is derived from a relatively large and well-characterized cohort. In addition, the results of the sensitivity analyses consistently generated the same result: those with metabolic syndrome had greater increasing UPDRS scores over time than those without metabolic syndrome. However, the conclusions are limited by the use of a modified definition of metabolic syndrome. Therefore, additional studies incorporating stricter measurements of the components of metabolic syndrome are required to confirm the findings of this initial study.

### Table 3 Change in motor UPDRS

<table>
<thead>
<tr>
<th>Effects</th>
<th>Estimate (SE)</th>
<th>95% CI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic syndrome</td>
<td>−0.4 (0.4)</td>
<td>−1.1 to 0.4</td>
<td>0.34</td>
</tr>
<tr>
<td>Time, y</td>
<td>0.8 (0.1)</td>
<td>0.6 to 1.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Metabolic syndrome × time</td>
<td>0.5 (0.2)</td>
<td>0.2 to 0.8</td>
<td>0.01</td>
</tr>
<tr>
<td>Uric acid, mg/dL</td>
<td>0.2 (0.1)</td>
<td>−0.1 to 0.4</td>
<td>0.14</td>
</tr>
</tbody>
</table>

Abbreviations: CI = confidence interval; SE = standard error; UPDRS = Unified Parkinson’s Disease Rating Scale.
In NET-PD LS1, participants meeting criteria for metabolic syndrome experienced a greater increase in total UPDRS scores, mainly due to increases in motor scores, compared to those not meeting these criteria. If confirmed, future work should determine whether treatment of metabolic syndrome results in a slower increase in UPDRS scores over time.

AUTHOR CONTRIBUTIONS

Maureen Lenkey, MD: study concept and design, interpretation of data, drafting/revising manuscript. Sheng Luo, PhD: analysis and interpretation of data, statistical analysis. Salomi Sharma, MBBS: study concept and design, interpretation of data, manuscript review. Anne-Marie A. Wills, MD, MPH: interpretation of data, revision of manuscript. Jacquelyn L. Bainbridge, BSPharm, PharmD, FCCP: study concept and design, interpretation of the data. Pei Shuenn Wong, PharmD, BCPS: study concept and data, interpretation of data. David K. Simon, MD, PhD: interpretation of data and review of manuscript. Jay Schneider, PhD: drafting/revising manuscript. Yunxi Zhang, MS: analysis and interpretation of data, statistical analysis. Adriana Pérez, MD, PhD: review and critique of statistical analyses, review and critique of manuscript. Rohit Dhall, MD, MSPH: interpretation of data and revising manuscript. Franca Cambi, MD, PhD: study design, writing of manuscript. James T. Boyd, MD: study concept and design, data collection, interpretation of the data.

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DISCLOSURE

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