Association of Metabolic Syndrome and Change in Unified Parkinson Disease Rating Scale Scores

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title character count: 93

number of references: 40
number of tables: 4

number of figures: 1

word count abstract: 250
word count paper: 2221

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Search terms words:
[165] Parkinson's disease/Parkinsonism, [146] All Medical/Systemic disease, [148] Endocrine

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Author disclosures:
Maureen Leehey, MD — Dr. Leehey reports no disclosures
Sheng Luo, PhD — Dr. Luo received grants from NIH, MDS, and CHDI Foundation
Saloni Sharma, MBBS — Dr. Sharma reports no disclosures
Anne-Marie A Wills, MD, MPH – Dr–Dr. Wills serves as a consultant for Accordant, Sage Bionetworks, and has received research support from the ALS Association, Pfizer and Acorda.
Jacquelyn L. Bainbridge, BSPharm, PharmD, FCCP — Dr. Bainbridge reports no disclosures
Pei Shieen Wong, PharmD, BCPS — Dr. Wong reports no disclosures
David Simon, MD, PhD — Dr. Simon reports no disclosures
Jay Schneider, PhD — Dr. Schneider reports no disclosures
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Adriana Pérez, MS, PhD — Dr. Perez reports no disclosures
Rohit Dhall, MD, MSPH – Dr–Dr. Dhall reports no disclosures
Chadwick W Christine, MD — Dr. Christine reports no disclosures
Carlos Singer, MD — Dr. Singer reports no disclosures
Franca Cambi, MD, PhD — Dr. Cambi reports no disclosures
James T Boyd, MD — Dr. Boyd served as a consultant and/or scientific advisor for AbbVie Inc., Auspex, Lundbeck, and Medical Education Resources; and received research support from Michael J. Fox Foundation, NIH/NINDS, Auspex, Biotie, CHDI Foundation, NeuroDerm, Chrono Therapeutics, Vaccinex

Study Funding:
NET-PD was funded by the NINDS: U01NS043127, U01NS043128, and U10NS44415-44555 from the National Institute of Neurologic Disorders and Stroke.

Abstract:

Objective

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

Methods

This is a secondary analysis of data from 1022 of 1741 participants of the NINDS Exploratory Trials in PD Long-term Study 1, a randomized, placebo-controlled trial of creatine in PD. Participants were categorized as having or not having metabolic syndrome based upon modified criteria from the National Cholesterol Education Program (NCEP) Adult Treatment Panel III. Those that had the same metabolic syndrome status at consecutive annual visits were included. The change in UPDRS and SDMT scores from randomization to three 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] years vs. 59.9 [9.4] years; $p<0.0001$), 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], women 4.9 [1.3] vs. 3.9 [0.9]; $p<0.0001$). 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] in motor UPDRS ($p=0.01$) scores compared with non-metabolic syndrome participants. There was no difference in the change in SDMT scores.

Conclusions

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

Introduction

Metabolic syndrome is a combination of conditions — hypertension , hyperglycemia, hyperlipidemia and increased waist circumference — that when occur together escalate a person's risk for heart disease, stroke, and diabetes. Recent studies suggest that the syndrome is also associated with increased risk of other diseases,[1-8] including Parkinson disease (PD).[1, 9] However, studies on the association of metabolic syndrome[10] or its components,[11-20] e.g. hyperglycemia or diabetes, and PD have yielded inconsistent results. For example, two recent meta-analyses of the association of diabetes and the risk of developing PD had opposite conclusions – one that diabetes increases risk of PD[21] and another that it does not.[22] Higher BMI in midlife, i.e., >25 kg/m^2, has been associated with an increased risk of PD in multiple studies[16, 18, 23] although not in others.[19, 24] A recent study found that PD patients with increasing BMI had slower PD progression than those with a stable or declining BMI[25] as measured by the Unified Parkinson Disease Rating Scale (UPDRS). Another study reported that diabetes was associated with more rigidity and a parkinsonian-type gait in aging persons without a diagnosis or PD or dementia.[26]

To our knowledge the effect of metabolic syndrome on PD progression has not previously been studied. The aim of this current study was to investigate the relationship between metabolic syndrome and progression of PD using change in UPDRS. Since since 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 NINDS 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 three years of the trial to those who were without evidence of metabolic syndrome.

Methods

Participants

NET-PD LS 1 was a large, multicenter, placebo-controlled, randomized, double-blinded trial of 10 mg of creatine monohydrate versus placebo and was conducted from March 2007 to September 2013. The study was terminated early, when an interim analysis determined creatine had no effect on progression of PD.[28] All participants had early stage PD and were on dopaminergic therapy at randomization. The study design and characteristics of the population have been reported previously.[27]

The NET-PD LS 1 study enrolled a total of 1741 participants. Each participant was categorized as having metabolic syndrome or not at baseline, one, two, and three-year visits. Due to missing data at any of these visits, we were unable to assess the metabolic syndrome status of 319 participants. Further, only those that maintained the same metabolic syndrome status for consecutive visits were included. 400 participants experienced a change in their metabolic syndrome status during the first three years of the study and were excluded from the analysis. Therefore, out of the 1741 participants at baseline, 1022 were included in the final analysis.

Standard Protocol Approvals, Registrations and Patient Consents

NET-PD LS 1 is registered on clinicaltrials.gov with identifier NCT00449865. The institutional review boards of each institution that participated approved the study, and all participants signed informed consent.

Outcome Measures

As part of NET-PD LS-1, UPDRS scores parts I, II, and III were assessed over time. Three outcome measures were used for this study from baseline to the three-year visit. The primary outcome measure was the change in the total UPDRS score (which we define here as parts I+II+III) from the baseline (randomization) to the three-year visit. The secondary outcome measure was the change in the motor UPDRS (part III) over the same time range. An additional outcome measure was the Symbol Digit Modalities Test (SDMT) score,[29] which was the only cognitive test collected at annual visits.

Exposure

We categorized participants based upon the commonly agreed-upon criteria from the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III), which was updated in 2005.[30] The NCEP criteria require three or more of the following to be diagnosed with metabolic syndrome: (1) waist circumference: women >35 inches, men >40 inches, (2) serum triglycerides ≥150 mg/dL (1.7 mmol/L) or medication therapy for high triglycerides, (3) serum high-density lipoprotein cholesterol <50 mg/dl (1.3 mmol/L) in women and <40 mg/dL (1 mmol/L) in men or medication treatment for low high-density lipoprotein cholesterol, (4) blood pressure ≥130/85 mmHg or on medication therapy for high blood pressure, and (5) fasting plasma glucose ≥100 mg/dL (5.6 mmol/L) or on medication therapy for high glucose.

Because the protocol for NET-PD LS 1 did not include waist measurements or collection of cholesterol, triglyceride, or fasting glucose levels, we adapted the ATP III criteria[30] for use in our study.[30] Metabolic syndrome was defined as having two or more of the following criteria: (1) body mass index (BMI)>30, (2) on statin medication, (3) either

systolic blood pressure >130, diastolic >85 or on anti-hypertensive medication, or (4) random blood sugar >120 mg/dl or on anti-hyperglycemic medication. Criteria were the same for both sexes. Participants who no longer fulfilled our modified criteria at subsequent visits were excluded from the analysis in order to avoid misclassification bias. Using these modified ATP III criteria, participants were classified into two groups: (1) participants who had metabolic syndrome throughout the three years of the study and (2) participants who were without evidence of metabolic syndrome across all three years.

Statistical Methods

Descriptive statistics (mean, standard deviation, frequency, and percentages) were used to summarize the demographics for two groups: metabolic syndrome and no metabolic syndrome. Difference in the mean or proportions between these two groups were checked by t-test or chi-square test.

The association of metabolic syndrome with the change in the total and motor UPDRS and SDMT scores across time was estimated utilizing a linear mixed model. Since the randomization process included blocking by site, the site and treatment assignment (creatine vs. placebo) were both used as covariates.[27]

Metabolic syndrome, time in years, treatment group, and the interaction term of metabolic syndrome and time in years were tested in this model after adjusting for confounding variables: baseline age, baseline total UPDRS, sex, handedness, race, uric acid levels, and disease duration at baseline. Similarly, a second model was adjusted for motor UPDRS and the only difference was the covariate baseline motor UPDRS instead of total UPDRS as stated before. A lowess plot for change in total UPDRS

across time is presented to show the differences by group. The SDMT analysis, using change in SDMT from baseline as the response variable, predictors of baseline SDMT, metabolic syndrome status, time in years, the interaction term of metabolic syndrome and time in years, was adjusted for confounding variables of baseline age, total UPDRS, gender, handedness, race, uric acid levels, and disease duration.

All statistical analyses were conducted using SAS statistical software (version 9.4; SAS Institute Inc).

Sensitivity Analyses

We considered alternative ways of analyzing the current data set. We looked at the entire NET-PD LS1 cohort, dividing the metabolic versus no metabolic syndrome groups according to their status at baseline, and followed them for their entire participation in the study, up to five 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 three or more of the four criteria, rather than two or more as in the presented data. Further, we ran the analyses with different criteria for metabolic syndrome, considering that if one was taking an anti-hypertensive, anti-hyperlipidemia, or anti-hypergylcemic medication that they would not meet that criterion for metabolic syndrome since the indication was adequately treated. Each of these sensitivity analyses produced the same results. Since the results were the same as those presented here, they are not shown but they are available upon request from the authors.

Results

Table 1 shows the demographic characteristics of the participants for this study according to whether or not participants were categorized as having metabolic syndrome. Baseline mean age and mean uric acid levels were significantly different in these two groups, as well as the proportion of men and women in these two groups. Participants with metabolic syndrome were more likely to be men, older, and have a higher mean uric acid level compared to those without metabolic syndrome.

Table 2 shows the change in total UPDRS over three 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 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 Figure 1, 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), the secondary outcome measure, over three years compared between the two 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.

Table 4 shows the change in SDMT. While the SDMT declined 0.2 units (SE=0.1) per year (p=0.03), there was no significant difference, 0.3 vs. 0.2 units annual decline, between those with vs. without metabolic syndrome (p=0.77), respectively.

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 over time compared to those without metabolic syndrome. This finding is consistent with prior studies suggesting that the presence of metabolic syndrome is associated with increased risk of developing PD, Alzheimers, cognitive decline and other diseases.[1-8] We could find no other study showing an association between metabolic syndrome and progression of PD, so this finding will need 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. Since 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 was not collected in the NET-PD study, so this theory cannot be substantiated with our data. Regarding blood trigyceride,[23] glucose,[23, 31] and HDL cholesterol levels, the literature to date is either conflicting, lacking, or not informative. Insulin resistance and inflammation underlie metabolic syndrome,[32] and these pathologic mechanisms also contribute to the progressive loss of dopaminergic cells that results in PD.[33, 34] 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 expression of insulin and insulin growth factors and their related receptors and CNS insulin resistence being reported in PD. Activites 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 alpha-synuclein[35, 36]. While further studies are needed to judge whether these brain abnormalities correlate with clinical longitudinal signs, given that PD patients have CNS insulin related abnormalities which normally play a protective role, concurrent metabolic syndrome is likely to exacerbate these baseline abnormalities and enhance progression of disease.

While uric acid levels are not a defined componenet of metabolic syndrome, the syndrome is associated with higher uric acid levels. Studies to date suggest that higher uric acid levels are associated with slower increasing UPDRS scores.[37, 38] 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. 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 which occurred in this early treated Parkinson's group.[39] Further, the SMDT evaluates attention and not other cognitive domains or global cognitive function.[40]

A strength of this study is that it is derived from a relatively large and well-characterized cohort. Also, the results of the sensitivity analyses generated the same results, that

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 will be required in order to confirm the findings of this initial study.

In conclusion, in NET-PD LS1, participants meeting criteria for metabolic syndrome experienced 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 if treatment of metabolic syndrome results in a slower increase in UPDRS scores over time.

Table 1. Baseline Characteristics of Participants (n=1022) by Metabolic Syndrome Status

Demographics	No Metabolic Syndrome (n=626) Mean (SD)	Metabolic Syndrome (n=396) Mean (SD)	*P* value
Age, years	59.9 (9.4)	63.9 (8.1)	<.0001
Male, No. (%)	357 (57.0)	298 (75.3)	<.0001
Disease duration, years	1.6 (1.1)	1.6 (1.1)	0.92
Total UPDRS, score	25.0 (10.7)	26.0 (10.7)	0.16
Motor UPDRS, score	17.0 (7.9)	17.7 (7.9)	0.14
Treatment: Creatine, No. (%)	310 (49.5)	188 (47.5)	0.52
Handedness: Right, No. (%)	560 (89.5)	352 (88.9)	
Handedness: Left/mixed, No. (%)	66 (10.5)	44 (11.1)	0.78
Race: White, No. (%)	586 (93.6)	365 (92.2)	0.38
Uric acid, men	5.3 (1.1)	5.7 (1.3)	<.0001
Uric acid, women	3.9 (0.9)	4.9 (1.3)	

Table 2. Change in total UPDRS

Effects	Estimate (SE)	95% CI	*P* value
Metabolic Syndrome[+]	-0.6 (0.5)	(-1.6 to 0.5)	0.30
Time (years)	1.7 (0.2)	(1.4 to 2.0)	<.0001
Metabolic Syndrome*Time	0.6 (0.2)	(0.1 to 1.0)	0.02
Uric Acid	0.2 (0.2)	(-0.1 to 0.5)	0.29

[+]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.

Table 3. Change in motor UPDRS

Effects	**Estimate (SE)**	**95% CI**	***P* value**
Metabolic Syndrome	-0.4 (0.4)	(-1.1 to 0.4)	0.34
Time (years)	0.8 (0.1)	(0.6 to 1.0)	<.0001
Metabolic Syndrome*Time	0.5 (0.2)	(0.2 to 0.8)	0.01
Uric Acid	0.2 (0.1)	(-0.1 to 0.4)	0.14

Figure 1: Lowess plot for change in total UPDRS. Sample size: 1022 (Assuming the duration of one month equal to 30.5 days)

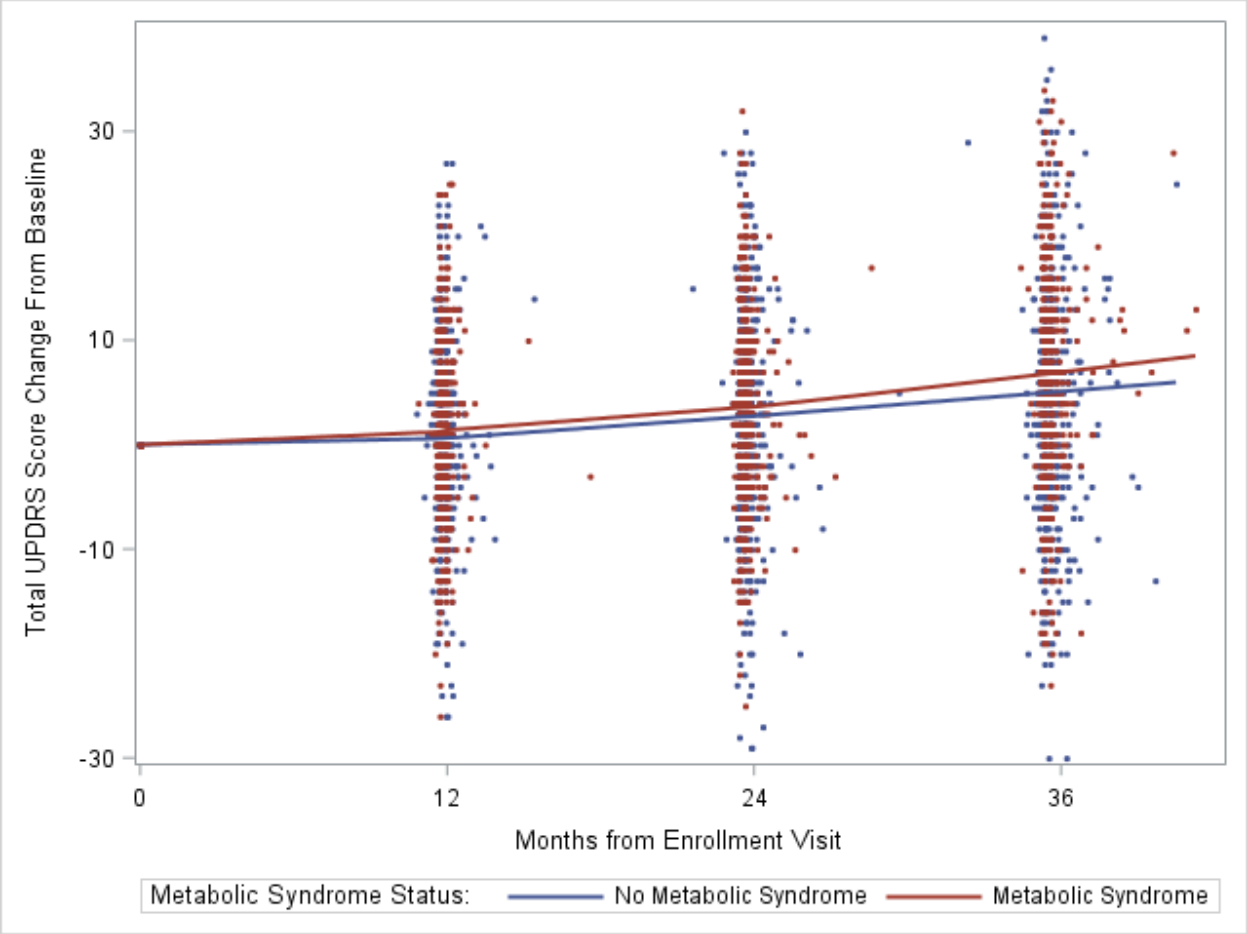

Table 4. Change in SDMT

Effects	**Estimate (SE)**	**95% CI**	***P* value**
Metabolic Syndrome[+]	0.2 (0.5)	(-0.7, 1.1)	0.65
Time (years)	-0.2 (0.1)	(-0.4, 0.1)	0.03
Metabolic Syndrome*Time	-0.1 (0.2)	(-0.5, 0.3)	0.77
Uric Acid	0.1 (0.1)	(-0.2, 0.3)	0.70
SDMT baseline	-0.2 (0.02)	(-0.2, -0.1)	<.0001

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