Can lifestyle modification slow progression of Parkinson disease?

Peter Hedera, MD, PhD
Thomas L. Davis, MD

Correspondence to
Dr. Hedera:
peter.hedera@vanderbilt.edu

Neurology® 2017;89:1760–1761

Parkinson disease (PD), similar to other neurodegenerative conditions, is characterized by relentless clinical progression with gradual worsening of both motor and nonmotor features. Potential neuroprotective therapies focusing on aspects of neurodegeneration in PD such as impaired mitochondrial function with abnormalities of oxidative phosphorylation, increased oxidative stress, and suppressed neuroinflammation, have failed to alter the clinical course of PD.[1,2] New insights into PD pathophysiology have identified potential molecular targets, including accumulation and potential prion-like spreading of aggregates containing misfolded α-synuclein protein.[3] These therapies are only approaching clinical testing, and their true therapeutic potential remains unknown. Even if successful, they are many years away from clinical availability. Thus, at present, we do not have any proven pharmacologic options to modify the progressive decline of patients with PD.

Although selective neurodegeneration of nigrostriatal dopaminergic neurons is widely accepted as a key feature of PD, additional pathologic changes may play a role in PD pathogenesis. Damage to the blood-brain barrier and cerebral microvascular changes have been implicated as potentially important factors in PD progression.[4] Microvascular damage may be a direct consequence of neurodegenerative processes, with endothelial damage from α-synuclein deposits aggravated by associated inflammatory reaction. Traditional cardiovascular risk factors, most notably hypertension and diabetes mellitus, also affect the cerebral microvasculature in PD. Moreover, the degree of these changes, assessed as leukoaraiosis on MRI, may contribute to the rate of progression in PD.[5] The frequency of midline problems affecting balance and gait was associated with a higher burden of white matter changes, suggesting that aggressive management of these risk factors may delay the onset of disabling postural changes in PD.[5,6]

Cardiovascular risk factors are important as possible modifiers of a neurodegenerative cascade, and their presence has been suggested as an independent risk factor of PD, together with genetic predispositions and environmental exposures.[7] Metabolic syndrome includes hypertension, insulin resistance with hyperglycemia, dyslipidemia with hypertriglyceridemia, elevated low-density lipoprotein and reduced high-density lipoprotein levels, and central obesity with increased waist circumference.[8] Patients with metabolic syndrome have an elevated risk of developing diabetes mellitus and having cardiovascular and cerebrovascular disease. While metabolic syndrome is firmly linked to an increased incidence of diabetes mellitus, stroke, and myocardial infarction, its role in other conditions is still debated. Previous studies in PD have yielded inconsistent results. Several investigations have reported an increased risk of PD in patients with metabolic syndrome. However, other studies did not confirm this finding when various components of metabolic syndrome were analyzed.[7,9]

While the possible contribution of metabolic syndrome to the onset of PD remains to be fully determined, its influence on the progression of PD has not been studied until the report in this issue of *Neurology*® by Leehey et al.[10] Using data from 1,022 participants in the National Institute of Neurological Disorders and Stroke Exploratory Trials in PD Long-Term Study 1 (NET-PD LS 1), they report a secondary analysis comparing the rate of progression of PD in patients with and without metabolic syndrome. The disease progression was measured by annual assessment of Unified Parkinson's Disease Rating Scale parts I through III, and cognitive status was assessed by the Symbol Digit Modalities Tests scores during 3 years of follow-up. The main finding of this study is a faster deterioration of motor function in patients who were classified as having metabolic syndrome and that these patients accrued an additional 0.5 point annually compared to patients without metabolic syndrome. Although the coexistence of metabolic syndrome may be a risk factor for cognitive decline, this study did not detect any difference in cognitive performance between the 2 groups.

The analysis has several important limitations that need to be considered. This was a secondary analysis of a study focused on possible neuroprotective role of creatine. The study protocol did not collect all data

See page 1789

From the Department of Neurology, Vanderbilt University Medical Center, Nashville, TN.

Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the editorial.

necessary for the assessment of metabolic syndrome, most notably a detailed lipid profile, fasting glucose, and waist circumference, and additional analysis of these factors for PD progression is not possible. Furthermore, the groups were not matched, with the metabolic syndrome cohort being older and having a greater proportion of men. This was corrected in the statistical analysis, but this finding needs to be replicated. Lastly, only those patients who maintained the same metabolic syndrome status during the whole study were included. Thus, we cannot assess whether the improvement of metabolic status altered the course of PD, and again, this needs to be addressed by a prospective study designed to show this possible difference.

Despite these limitations, this is an important study further strengthening the connection between metabolic syndrome and PD. The neurologists treating patients with PD may wonder whether they have enough evidence to support the active and aggressive control of metabolic syndrome in patients with PD. The first step in management of metabolic syndrome is lifestyle modification with dietary changes and regular exercise.[8] Several studies have shown the benefits of regular physical activity in patients with PD, even though this was not analyzed in the context of coexisting metabolic syndrome.[11,12] Thus, increased physical activity on a regular basis has a potential to improve PD and metabolic syndrome, and this should be reviewed with every patient with PD.

The role of neurologists in PD treatment is ever increasing, and we moved from the treatment of movement disorder only to a complex management of both motor and multiple nonmotor symptoms. The emerging data support the fact that we need to expand our roles consistently to include coaching of lifestyle changes and active management of various features of metabolic syndrome if present.

STUDY FUNDING

No targeted funding reported.

DISCLOSURE

Both authors have nothing to disclose. Go to Neurology.org for full disclosures.

REFERENCES

1. Dias V, Junn E, Mouradian MM. The role of oxidative stress in Parkinson's disease. J Parkinsons Dis 2013;3:461–491.
2. Hirsch EC, Vyas S, Hunot S. Neuroinflammation in Parkinson's disease: a target for neuroprotection? Lancet Neurol 2009;8:382–397.
3. Guo JL, Lee VM. Cell-to-cell transmission of pathogenic proteins in neurodegenerative diseases. Nat Med 2014;20:130–138.
4. Lee H, Pienaar IS. Disruption of the blood-brain barrier in Parkinson's disease: curse or route to a cure? Front Biosci (Landmark Ed) 2014;19:272–280.
5. Kotagal V, Albin RL, Müller ML, et al. Modifiable cardiovascular risk factors and axial motor impairments in Parkinson disease. Neurology 2014;82:1514–1520.
6. Hedera P, Friedman JH. Can fall of blood pressure prevent falls in Parkinson disease? Neurology 2014;82:1488–1489.
7. Simon KC, Chen H, Schwarzschild M, Ascherio A. Hypertension, hypercholesterolemia, diabetes, and risk of Parkinson disease. Neurology 2007;69:1688–1695.
8. Alberti KG, Eckel RH, Grundy SM, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation 2009;120:1640–1645.
9. Sääksjärvi K, Knekt P, Männistö S, Lyytinen J, Heliövaara M. Prospective study on the components of metabolic syndrome and the incidence of Parkinson's disease. Parkinsonism Relat Disord 2015;21:1148–1155.
10. Leehey M, Luo S, Sharma S, et al. Association of metabolic syndrome and change in Unified Parkinson's Disease Rating Scale scores. Neurology 2017;89:1789–1794.
11. Rafferty MR, Schmidt PN, Luo ST, et al. Regular exercise, quality of life, and mobility in Parkinson's disease: a longitudinal analysis of National Parkinson Foundation Quality Improvement Initiative Data. J Parkinsons Dis 2017;7:193–202.
12. LaHue SC, Comella CL, Tanner CM. The best medicine? The influence of physical activity and inactivity on Parkinson's disease. Mov Disord 2016;31:1444–1454.