MAYO CLINIC

Aerobic Exercise: Evidence for a Direct Brain Effect to Slow Parkinson Disease Progression

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Abstract

No medications are proven to slow the progression of Parkinson disease (PD). Of special concern with longer-standing PD is cognitive decline, as well as motor symptoms unresponsive to dopamine replacement therapy. Not fully recognized is the substantial accumulating evidence that long-term aerobic exercise may attenuate PD progression. Randomized controlled trial proof will not be forthcoming due to many complicating methodological factors. However, extensive and diverse avenues of scientific investigation converge to argue that aerobic exercise and cardiovascular fitness directly influence cerebral mechanisms mediating PD progression. To objectively assess the evidence for a PD exercise benefit, a comprehensive PubMed literature search was conducted, with an unbiased focus on exercise influences on parkinsonism, cognition, brain structure, and brain function. This aggregate literature provides a compelling argument for regular aerobic-type exercise and cardiovascular fitness attenuating PD progression.

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Parkinson disease (PD) is a relatively common neurologic condition with perhaps 1 million affected people in the United States. Increasingly, their treatment is falling into the hands of primary care physicians, who should be able to provide optimal care to most patients.[1-3] As previously described,[2] appropriate carbidopa/levodopa administration is the single most crucial medication strategy. Herein, the argument is advanced that the other important component of optimal PD treatment is engagement in regular aerobic-type exercise. Although no medications are proven to slow PD progression, there is substantial evidence for vigorous exercise attenuating PD progression, which is the specific focus of this article.

Exercise advice may be skeptically viewed by patients. The lay public is bombarded by health advice, some biologically supported and some that is arbitrary, unsupported, or commercially driven. Exercise is easily dismissed as yet another dictum from health experts. Moreover, regular exercise implies strenuous, time-consuming physical work, which for some people is novel. Thus, an exercise prescription for people with PD is easily discarded, especially in the absence of definite proof.

IMPEDIMENTS TO CLINICAL TRIAL ASSESSMENT OF PD EXERCISE INFLUENCES

Definitive arguments for any health intervention are expected to come from clinical randomized controlled trials (RCTs). The outcome of interest is preventing the slow neurologic decline that occurs with PD. Unfortunately, a valid and reliable RCT of long-term exercise to slow PD progression is not truly feasible for several reasons.

First, PD progression tends to be very slow. Reliable and valid biomarkers of PD progression have yet to be developed. Assessment requires outcome measures that will not be contaminated by medication effects (ie, levodopa and related drugs); this precludes motor outcomes routinely used in PD clinical trials (eg, Unified Parkinson Disease Rating Scale scores). From a patient's perspective, the most important markers of clinical progression are dementia and levodopa-refractory symptoms, which are measureable and not subject to medication influences. However, these problems typically do not develop for many years or decades and, thus, are not amenable to RCTs.

Second is the physical and motivational challenge of longer-term engagement in an

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aerobic exercise program. Long-term adherence to a rigorous exercise protocol among senior patients with PD is potentially problematic.

Third, confirmation of exercise effort in such a clinical trial is not easily assessed, although cardiovascular fitness is an objective outcome of long-term aerobic exercise. Not to be overlooked in such clinical trials is off-protocol exercise in the "sedentary" control patients cognizant of the study hypothesis that exercise may slow PD progression.

THE RATIONALE FOR THIS REVIEW

Definitive proof of exercise slowing PD progression is unlikely to be forthcoming from RCTs because of the previously mentioned methodological problems. However, there is a very extensive and diverse literature relating to direct exercise influences in the brain, relevant to PD. At an elementary level, this includes exercise-induced brain neuroplasticity, maintenance of synaptic connections, and preservation of brain integrity. Macroscopically, exercise influences on brain integrity are now measureable with modern brain magnetic imaging technology.

The goal of this article is to review the evidence for long-term aerobic-type exercise as a means for slowing PD progression. Although exercise is well-recognized to attenuate brain atherosclerotic risks (ie, cerebrovascular disease), this focus will be on direct brain influences of aerobic-type exercise. Because subject reviews tend to have agendas that may bias interpretation, a concerted effort was made to survey the entire published literature identified in a PubMed search and report both positive and negative findings. The intent is to provide clinicians with the evidence needed for counseling their patients with PD.

METHODS: LITERATURE SEARCH

This PubMed literature search was performed using 2 search term strategies: *exercise and Parkinson disease* and *exercise and cognition. Cognition* was chosen because cognitive impairment/dementia is perhaps the most feared outcome of patients with PD. All the titles from this literature search to January 15, 2017, were reviewed, and relevant papers were read. Mixed results and negative trials are cited in this review. The reference list contains all the relevant papers; however, individual studies are not separately addressed when included in cited meta-analyses.

Included in this review are adult human (age >18 years) and animal studies. Aerobic-type exercise was the focus because a preliminary reading of this literature indicated that this is the most robust and comprehensive component of this exercise literature. It also allowed extension to animal studies, where running exercise is a common experimental variable. Although resistance exercise might be relevant to this topic, preliminary review of resistance exercise publications suggested too few articles and too varied methods to reliably assess. Papers reporting exercise outcomes in nonrelevant disease groups were excluded (eg, patients with diabetes, cancer, etc). Only studies of long-term exercise were included, excluding short-term exercise trials. Studies using outcome measures that could be influenced by symptomatic drug treatment were excluded (eg, carbidopa/levodopa for PD). The PubMed search targeting *exercise and Parkinson disease* yielded 1781 titles; *exercise and cognition* yielded 5054 titles.

ARTICLE HIGHLIGHTS

- Parkinson disease is a slowly progressive neurodegenerative condition; after many years, dementia or medication-refractory motor symptoms may develop.
- A myriad of animal studies document a direct, favorable effect of aerobic-type exercise on the brain; this includes liberation of neurotrophic hormones and enhancement of a variety of neuroplasticity mechanisms. Exercise tends to protect animals from neurotoxins that induce parkinsonism.
- Long-term exercise and fitness in healthy humans is associated with greater volumes of cerebral cortex and hippocampus and less age-related white matter pathology.
- Midlife exercise is associated with a significantly reduced later risk of Parkinson disease.
- Conclusion from this evidence: Regular aerobic-type exercise tending to lead to fitness is the single strategy with compelling evidence for slowing Parkinson disease progression. All patients with Parkinson disease should be encouraged to engage in regular such exercise.