

The evolution of mild parkinsonian signs in aging

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Abstract The progression of mild parkinsonian signs in the absence of idiopathic Parkinson's disease in aging is unclear. This study aims to identify predictors of the evolution of mild parkinsonian signs in non-demented older adults. Two hundred ten participants (76.25 ± 7.10 years, 57 % women) were assessed at baseline and 1-year follow-up. Mild parkinsonian signs were defined as the presence of bradykinesia, rigidity and/or rest tremor. Depending upon the presence of these features at baseline and follow-up, participants were divided into one of four groups (no, transient, persistent or new-onset mild parkinsonian signs). Physical function was assessed using gait velocity. Ninety-five participants presented with mild parkinsonian signs at baseline. At 1-year follow-up, 59 demonstrated persistent mild parkinsonian signs, while 36 recovered (i.e., transient). Participants with persistent mild parkinsonian signs were older (79.66 ± 7.15 vs. 75.81 ± 7.37 years, $p = 0.01$) and evidenced slower gait velocity (90.41 ± 21.46 vs. 109.92 ± 24.32 cm/s, $p < 0.01$) compared to those with transient mild parkinsonian signs. Gait velocity predicted persistence of mild parkinsonian signs, even after adjustments (OR: 0.96, 95 % CI: 0.94–0.98).

Fifty-five participants demonstrated new-onset of mild parkinsonian signs. In comparison to participants without mild parkinsonian signs, presence of cardiovascular but not cerebrovascular disease at baseline was associated with new-onset mild parkinsonian signs. Our study reveals that gait velocity was the main predictor of persistent mild parkinsonian signs, whereas cardiovascular disease was associated with new-onset mild parkinsonian signs. These findings suggest a vascular mechanism for the onset of mild parkinsonian signs and a different mechanism, possibly neurodegenerative, for the persistence of mild parkinsonian signs.

Keywords Mild parkinsonian signs · Aging · Gait · Cardiovascular disease · Cerebrovascular disease

Introduction

Mild parkinsonian signs (MPS) are common in aging even in the absence of idiopathic Parkinson's disease (PD), with a wide variance in prevalence ranging from 15 to 52 % [1, 2]. Age, criteria employed to define MPS, and cognitive status likely explain the large discrepancy in reported prevalence rates. In previous studies, MPS were associated not only with vascular risk factors [3], depression [4], dementia [5–7], and mortality [1, 8, 9], but also with functional disability [10, 11]. Among functional disability, the use of walking aids was associated with MPS [2].

While previous longitudinal studies have established the relationship of MPS with incident dementia in aging [6, 7, 12, 13], their association with other important clinical outcomes like gait disorders or cardiovascular conditions has not been documented. Recently cerebrovascular lesions,

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including macro and microinfarcts, were associated with MPS and with parkinsonian gait [14]. Besides vascular lesions and dementia, a pathological study of 744 deceased participants with antemortem MPS assessment demonstrated that nigral neuronal loss, but not nigral Lewy bodies deposition was associated with MPS [15]. However, to our knowledge no study to date has identified risk factors associated with the progression of MPS in aging.

To address this knowledge gap, we conducted a prospective cohort study investigating predictors of MPS in community residing non-demented older adults without PD or other parkinsonian syndromes assessed at baseline and at 1-year follow-up. We hypothesized that vascular pathophysiological mechanisms would be associated with the presence of MPS in the elderly, but the contribution of additional factors related with neurodegenerative processes, would be more likely in older adults with persistent MPS at follow-up.

Methods

Participants

Four hundred thirty-nine non-demented adults aged 65 and older were recruited in an ongoing cohort study entitled Central Control of Mobility in Aging (CCMA) from June 2011 to November 2013, and of whom 264 completed a 1-year follow up. The CCMA longitudinal study aims to determine cognitive and brain predictors of mobility decline and disability in aging. The study procedure has been previously described [16, 17]. Briefly, participants enrolled in the CCMA study are non-demented older adults residing in lower Westchester County who have successfully passed a telephone-screening interview. Participants engage in two in-house evaluations per year, where they receive comprehensive neurological, neuropsychological, and physical examinations. Consensus diagnostic case conferences were conducted to assure that participants did not meet criteria for dementia [18]. Of the 264 participants who completed the 1-year follow-up evaluation, participants without complete neurological examinations ($n = 37$), idiopathic PD at baseline ($n = 7$), missing quantitative gait assessments at baseline ($n = 6$), or prescribed dopamine-blocking agents/neuroleptics ($n = 4$) were excluded from this analysis. Following exclusions, 210 non-demented older adults were included in the current analysis (mean age: 76.25 ± 7.10 years, 57 % women). The institutional review board of the Albert Einstein College of Medicine approved the experimental procedures and all participants provided written informed consent in accordance with the tenets of the Declaration of Helsinki.

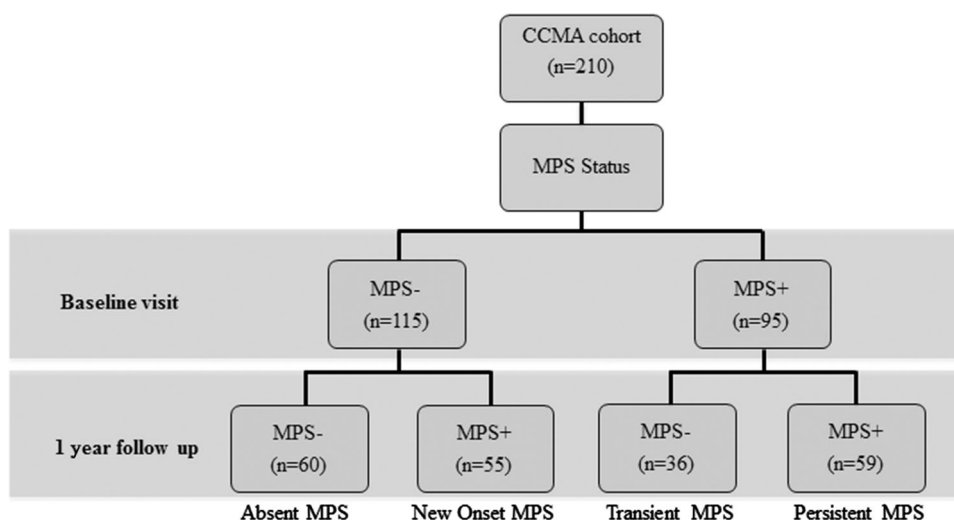
Mild parkinsonian signs and clinical assessment

Comprehensive neurological examination included assessment for clinical gait abnormalities [19], MPS, and medical illnesses. MPS were systematically ascertained in participants by the clinician using the motor evaluation portion (Part III) of the original version of the Unified Parkinson's Disease Rating Scale (UPDRS) [20]. Severity indices for individual MPS were calculated by summing clinician ratings (0–4) within 3 core domains: (1) bradykinesia in extremities and body (UPDRS#23-26, 31); (2) rigidity in extremities and neck (UPDRS#22); and (3) rest tremor in extremities (UPDRS#20). A total MPS score was subsequently created, both at baseline and at follow-up, by adding the severity indices of the individual MPS. As in our previous work, we aimed to identify early markers of abnormal motor aging by taking a sensitive approach to define MPS based on the presence of any one feature of MPS [21], but more stringent methods have previously been employed [7, 10]. For the MPS severity score, the Cronbach's α of 0.85 indicated good internal consistency, with excellent internal consistency for bradykinesia (0.90) and tremor (0.90), and good internal consistency for rigidity (0.88). The inter-rater reliability of MPS across the two clinicians revealed good inter-rater reliability (kappa, 0.60–0.90).

Of the 210 participants, 95 had MPS and 115 had no MPS at baseline. We examined the evolution of MPS in this cohort, by dividing participants with MPS at baseline (e.g., MPS+) into two groups: (i) MPS at baseline and at 1-year follow-up (persistent MPS group) and (ii) MPS at baseline but not at 1-year follow-up (transient MPS group). Further, to investigate potential contributors to MPS development, we divided participants without MPS at baseline (e.g., MPS–) into two groups: (iii) no MPS at baseline and at 1-year follow-up (absent MPS group) and (iv) no MPS at baseline and onset of new MPS at 1-year follow-up (new onset MPS group; Fig. 1).

The clinician documented the presence of depression, medical illnesses, cardiovascular disease, cerebrovascular disease, and cardiovascular risk factors, as these have been previously associated with MPS [22]. The geriatric depression scale (GDS [23]) was used to measure depression. Global health status summary scores (range 0–10) were obtained from dichotomous rating of diabetes, chronic heart failure, arthritis, hypertension, depression, stroke, Parkinson's disease, chronic obstructive pulmonary disease, angina, and myocardial infarction [24, 25]. History of vascular diseases and medical illnesses were obtained through clinical interview. Vascular diseases were categorized as vascular risk factors (any one of diabetes, hypertension, hypercholesterolemia, BMI > 30, and smoking), cardiovascular disease (any one of myocardial

Fig. 1 Classification of eligible participants based on MPS status. Flowchart of CCMA participants based on presence or absence of mild parkinsonian signs at baseline and 1-year follow-up



CCMA= Central Control of Mobility in Aging study; MPS=Mild Parkinsonian Signs

infarction, angina, arrhythmia, and chronic heart failure), and cerebrovascular disease (any one of stroke or transient ischemic attacks). Vascular severity scores were also calculated by summing the presence of conditions within each of the three vascular domains.

Physical and cognitive function

Quantitative gait assessments were conducted by a research assistant (blinded to the MPS status) as described in our previous studies [24, 26, 27]. Gait velocity (cm/s) was measured using an instrumented walkway with embedded pressure sensors (GAITRite, CIR Systems, Havertown, PA). The GAITRite system is widely used in clinical and research settings and has excellent psychometric properties. For the purposes of this study, we only report gait velocity because it can be measured ubiquitously with a stopwatch over a fixed distance and does not require the use of instrumented methods.

Global cognitive status was assessed using Repeatable Battery for Assessment of Neuropsychological Status (RBANS) total score. The RBANS, a brief cognitive test with alternate forms, measures immediate and delayed memory, attention, language, and visuo-spatial abilities, which also provides a total index score [28].

Statistics

Descriptive statistics (mean and SD) were calculated for all four MPS groups. Data were inspected descriptively and graphically and the normality of model assumptions was formally tested. Separate analyses were conducted for individuals with and without MPS at baseline. That is,

within the MPS– group, individuals who never demonstrated MPS (e.g., absent group) were compared to those who developed MPS at follow-up (e.g., new onset MPS group). Similarly, within the MPS+ group, those that continued to demonstrate MPS at 1-year follow-up (e.g., persistent MPS group) were compared to those who did not demonstrate MPS at follow-up (e.g., transient MPS group).

Differences between groups were assessed using independent *t* tests and Bonferroni corrections were applied to account for multiple comparisons within each domain (e.g., demographics, MPS, vascular, and physical function indices, Table 1). Binary logistic regression analyses were subsequently performed to examine the association of persistent vs. transient MPS (independent variables) with gait velocity, health, vascular, depression, and RBANS total scores (dependent variables) using SPSS version 20 [29]. Unadjusted univariate regressions were conducted first, followed by multivariate regressions adjusted for both age and gender. Similar univariate and multivariate regressions were also conducted for the absent vs. new onset MPS comparison groups.

Results

Baseline characteristics of the sample are provided in Table 1 for individuals with persistent and transient MPS and in Table 2 for those with absent and new onset MPS. Regardless of MPS classification, individuals were deemed relatively healthy and cognitively intact as determined by their global health status (GHS) and RBANS total score. Within the MPS + groups, rigidity was the most common MPS at baseline, followed by bradykinesia, and rest tremor

Table 1 Baseline characteristics for individuals with MPS

	Persistent (n = 59)	Transient (n = 36)	p value
Demographics			
Age (years)	79.66 (7.15)	75.81 (7.37)	0.01
Education (years)	13.95 (3.21)	15.39 (2.71)	0.03
% Female	57.00	47.00	0.32
GHS score (0–10)	1.70 (1.10)	1.75 (1.03)	0.81
GDS score (0–30)	5.54 (4.05)	3.94 (3.22)	0.04
MPS Indices			
Bradykinesia (% present)	53.00	17.00	<0.01
Rigidity (% present)	83.00	83.00	0.97
Tremor (% present)	9.00	8.00	0.98
Vascular			
Vascular risk factor (0–5)	1.89 (0.98)	1.90 (1.27)	0.97
Cardiovascular conditions (0–4)	0.25 (0.50)	0.42 (1.25)	0.43
Cerebrovascular conditions (0–2)	0.08 (0.28)	0.12 (0.33)	0.59
Physical and cognitive function			
Gait velocity (cm/s)	90.41 (21.46)	109.92 (24.32)	<0.01
RBANS total score	90.36 (12.62)	94.19 (11.92)	0.15

MPS Mild Parkinsonian signs, GHS Global Health Score, GDS Geriatric Depression Scale, RBANS Repeatable Battery for the Assessment of Neuropsychological Status, p values presented in bold survive Bonferroni correction

(Table 1). Results from logistic regression adjusted for age and gender revealed that the presence of bradykinesia significantly predicted inclusion in either the transient or persistent MPS group (OR = 0.11, p < 0.01).

Of the 95 participants with MPS at baseline, 66 had one MPS and 29 had two MPS. To further confirm the association between MPS status and gait velocity, we conducted a sensitivity analysis using more stringent criteria to determine persistent vs. transient MPS status by requiring the presence of any two (instead of just one) features of MPS at baseline and at follow-up to define persistence. Participants with two features of MPS at baseline but none or one feature of MPS at follow-up were considered in the control group in this sensitivity analysis. Using the same multivariate logistic regression analysis, results confirmed that only gait velocity significantly predicts the progression of MPS (OR = 0.97, p = 0.02), even after controlling for age and gender. Differences in gait velocity were noted at baseline (t = 4.09, p < 0.001) and at follow-up (t = 4.09, p < 0.001) between transient and persistent MPS groups (Fig. 2).

Regarding new onset MPS, comparisons between the absent vs. new onset MPS groups revealed that participants

Table 2 Baseline characteristics for individuals without MPS

	Absent (n = 60)	New onset (n = 55)	p value
Demographics			
Age (years)	74.12 (5.88)	75.22 (6.93)	0.36
Education (years)	14.40 (2.54)	15.04 (3.48)	0.26
% Female	57.00	64.00	0.45
GHS score (0–10)	1.23 (0.93)	1.47 (1.27)	0.26
GDS score (0–30)	3.50 (2.33)	4.20 (3.36)	0.20
Vascular			
Vascular risk factor (0–5)	1.43 (1.06)	1.45 (1.12)	0.92
Cardiovascular conditions (0–4)	0.08 (0.33)	0.27 (0.49)	0.02
Cerebrovascular conditions (0–2)	0.03 (0.18)	0.19 (0.39)	0.21
Physical and cognitive function			
Gait velocity (cm/s)	108.56 (23.22)	101.15 (23.95)	0.10
RBANS total score	90.36 (12.62)	94.19 (11.92)	0.15

MPS Mild Parkinsonian signs, GHS Global Health Score, GDS Geriatric Depression Scale, RBANS Repeatable Battery for the Assessment of Neuropsychological Status, p value presented in bold survives Bonferroni correction

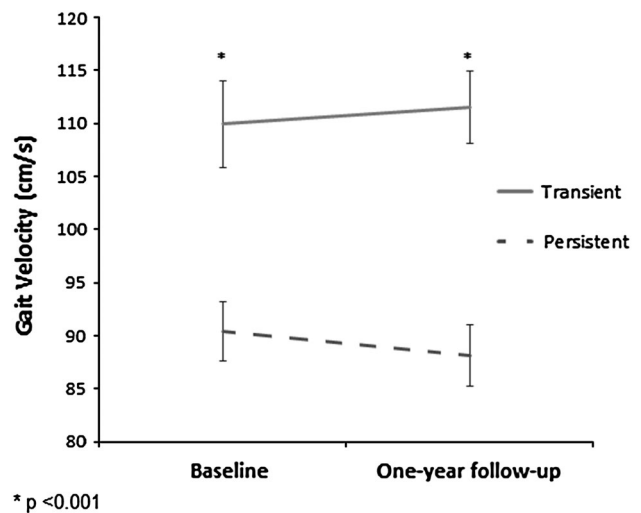


Fig. 2 Evolution of Gait Velocity for individuals with transient and persistent mild parkinsonian signs. A depiction of gait velocity for the 95 individuals with transient and persistent mild parkinsonian signs at baseline and 1-year follow up. Participants in transient group (solid grey trace) improved their gait velocity over 1 year from 110 to 112 cm/s, whereas those in the persistent group (dashed grey trace) decreased their gait velocity from 90 to 88 cm/s. Bars represent standard errors of the mean

in the new onset group demonstrated significantly more cardiovascular disease than those in the absent group (Table 3). This significant difference in severity of

Table 3 Predictors of persistent vs. transient mild parkinsonian signs

Variable	Univariate				Multivariate			
	Odds ratio	95 % C.I.		<i>p</i> value	Odds ratio	95 % C.I.		<i>p</i> value
		Lower	Upper			Lower	Upper	
Age, years	1.08	1.01	1.15	0.02	1.04	0.97	1.12	0.26
Gender (female)	1.52	0.66	3.50	0.33	1.67	0.62	4.50	0.31
GHS (0–10)	0.95	0.65	1.41	0.81	0.67	0.35	1.25	0.67
GDS (0–30)	1.13	1.00	1.29	0.06	1.11	0.96	1.28	0.16
Vascular risk factor (0–5)	1.01	0.70	1.44	0.97	1.16	0.68	2.00	0.59
Cardiovascular conditions (0–4)	1.25	0.69	2.27	0.45	1.22	0.61	2.43	0.58
Cerebrovascular conditions (0–2)	1.48	0.36	6.13	0.59	2.13	0.38	13.88	0.36
Gait velocity (cm/s)	0.96	0.94	0.98	<0.01	0.97	0.94	0.99	<0.01
Cognition (RBANS Total Score)	0.97	0.94	1.01	0.15	0.99	0.95	1.03	0.55

Table 4 Predictors of absent vs. new onset mild parkinsonian signs

Variable	Univariate				Multivariate			
	Odds ratio	95 % C.I.		<i>p</i> value	Odds ratio	95 % C.I.		<i>p</i> value
		Lower	Upper			Lower	Upper	
Age, years	1.03	0.97	1.09	0.36	0.99	0.92	1.06	0.78
Gender (female)	1.34	0.63	2.83	0.45	1.25	0.56	2.80	0.59
GHS (0–10)	1.22	0.87	1.71	0.25	1.00	0.58	1.72	1.00
GDS (0–30)	1.09	0.96	1.24	0.19	1.10	0.95	1.28	0.20
Vascular risk factor (0–5)	1.01	0.73	1.43	0.92	0.95	0.58	1.55	0.83
Cardiovascular conditions (0–4)	3.31	1.17	9.36	0.02	3.59	1.14	11.30	0.03
Cerebrovascular conditions (0–2)	2.90	0.54	15.61	0.22	2.34	0.32	16.96	0.40
Gait velocity (cm/s)	0.99	0.97	1.00	0.10	0.99	0.97	1.01	0.37
Cognition (RBANS total score)	0.98	0.95	1.02	0.35	0.99	0.95	1.02	0.43

Unadjusted univariate and multivariate regressions were performed to examine associations of MPS status (independent variables) with gait velocity, health (GHS), depression (GDS), vascular risk factors, cardiovascular disease, cerebrovascular disease, and cognition (dependent variables). Bold values indicate significant *p* values

GHS Global Health Score, GDS Geriatric Depression Scale, RBANS Repeatable Battery for the Assessment of Neuropsychological Status

cardiovascular disease persisted at both the univariate (OR = 3.31, *p* = 0.02) and multivariate levels (OR = 3.59, *p* = 0.03; Table 4).

Discussion

Our study shows that MPS is transient in 38 % of healthy older adults, and that gait velocity predicts MPS stability. Furthermore, the presence of cardiovascular disease, but not gait velocity or other selected predictors, was associated with the onset of new MPS at 1-year follow-up.

The etiopathogenesis of MPS is unclear in the elderly, and seems to be multifactorial [22]. MPS could represent an early marker of neurodegenerative disorders like PD or Alzheimer's disease (AD), a signature of small vascular infarcts [22], or a feature of neuronal loss in the

dopaminergic system as suggested by a recent neuropathological study [15]. Although none of these previously suggested causes are reversible, more than one-third of the participants in our study did not present with any MPS at the 1-year follow-up visit. Disappearance of MPS could be attributed to brain plasticity in normal older adults, as the CCMA cohort does not include participants with dementia at baseline. Unfortunately, information on interval rehabilitative efforts that might influence brain recovery and account for the disappearance of MPS in our participants was not available. The potential reversibility of MPS is important to consider for clinicians, because it could suggest that MPS does not necessarily foreshadow an immediate progressive condition.

Among the selected potential predictors of progressive MPS, only gait velocity was associated with persistent MPS at 1-year, even after using more stringent criteria for

defining the transient and persistent groups. Gait velocity in the elderly represents a final pathway combining balance, motor, sensory systems, as well as cognition [30]. In addition, the fact that gait velocity predicted persistent MPS is supported by recent findings in non-demented older adults without idiopathic PD: bradykinesia that represents a required feature for parkinsonism has been associated with gait velocity [21]. From a metabolic perspective, gait speed was associated with cholinergic but not dopaminergic denervation in PD patients; [31] suggesting a close relationship between gait and the cholinergic system. No other suspected risk factors than gait speed predicted the persistence of MPS.

In a similar longitudinal aging study investigating MPS and other predictors of dementia, Louis et al. [12] revealed that only MPS predicted dementia, but did not find an interaction with other known risk factors for dementia, including vascular risk factors or APOE- ϵ 4 positive status. Although previous studies have shown that the presence of MPS in non-demented older adults predicted incident dementia [6, 7, 12], cognitive function did not predict the stability nor the appearance of MPS in the present study. This could be explained by the fact that our definition of MPS purposefully did not include the postural instability and gait disturbance (PIGD) items from the UPDRS that were the main contributing factor for incident dementia in the religious order study [6]. Finally, the number of included participants in the present study is likely not large enough to show such a prediction. Taken together, the absence of vascular risk factors as predictors of persistent MPS and the progression of declines in gait velocity could suggest the contribution of underlying neurodegenerative processes, like PD, AD, or other non-vascular parkinsonian syndromes in the persistent MPS group.

The clinical profile of the MPS between the persistent and transient groups was different. Although rigidity was present in 83 % of participants in both groups, bradykinesia was the discriminative feature between the two groups, with the highest prevalence in the persistent group. Interestingly, in a study examining the association of MPS and white matter disease in the elderly, bradykinesia was independently related with the presence of the lacunar infarcts [32]. Regarding the complex link between MPS and cerebrovascular disease, the presence of cerebrovascular disease did not predict the stability or onset of new MPS, whereas cardiovascular disease did predict the new onset of MPS. Cardiovascular conditions, like atrial fibrillation, precede cerebrovascular conditions and constitute very well known risk factors for cerebrovascular conditions [33]. This chronological sequence could explain why cardiovascular but not cerebrovascular diseases

predict MPS. An alternative explanation could refer to the fact that cardiovascular diseases outweigh cerebrovascular diseases. Regarding the pathophysiology of vascular parkinsonism and its high prevalence in older adults [34], it is likely that vascular mechanisms are key contributors to the appearance of MPS in aging.

As a limitation, the short follow-up period and the relative small sample size, especially in the transient MPS group, could mask some additional predictors, like cognitive functions. These results should be replicated in a larger prospective cohort with longer follow-up intervals. In addition to the good internal consistency and inter-rater reliability of MPS in this study, the differences observed at baseline between the transient and persistent MPS groups (i.e. slower gait velocity in the persistent group compared to the transient group); the fact that applying more stringent criteria does not modify the results; and the fact that gait velocity decreases in the persistent group and increases in the transient group all suggest that our findings are consistent and not due to a reliability issue.

In conclusion, we observed that MPS may be reversible in the elderly and that gait velocity predicts the progression of MPS. Regarding new onset of MPS in aging, cardiovascular disease constitutes the main predictor. Our results suggest vascular mechanisms as the trigger of MPS in aging that are potentially reversible. However, for the progression of MPS, additional investigations are required to determine the pathophysiological mechanisms, possibly neurodegenerative, underlying gait velocity.

Highlights

- 1) MPS can be reversible in healthy older adults.
- 2) Slow gait velocity was the main predictor of persistent MPS in normal aging.
- 3) Cardiovascular disease was associated with onset of new MPS.

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Conflicts of interest No competing interests to report.

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Ethical standards The institutional review board of the Albert Einstein College of Medicine approved the experimental procedures and all participants provided written informed consent in accordance with the tenets of the Declaration of Helsinki.

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