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Research Article

Endothelial Progenitor Cell Levels Predict Future Physical Function: An Exploratory Analysis From the VA Enhanced Fitness Study

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Abstract

Background. Levels of circulating progenitor cells (CPCs) are depleted with aging and chronic injury and are associated with level of physical functioning; however, little is known about the correlation of CPCs with longer-term measures of physical capabilities. We sought to determine the association of CPCs with future levels of physical function and with changes in physical function over time.

Methods. CPCs were measured in 117 participants with impaired glucose tolerance in the Enhanced Fitness clinical trial based on the cell surface markers CD34 and CD133 and aldehyde dehydrogenase (ALDH) activity at baseline, 3 months, and 12 months. Physical function was assessed using usual and rapid gait speed, 6-minute walk distance, chair stand time, and SF-36 physical functioning score and reassessed at 3 and 12 months after clinical intervention.

Results. Higher baseline levels of $CD133^+$, $CD34^+$, $CD133^+CD34^+$, and $ALDH^{br}$ were each highly predictive of faster gait speed and longer distance walked in 6 minutes at both 3 and 12 months. These associations remained robust after adjustment for age, body mass index, baseline covariates, and inflammation and were independent of interventions to improve physical fitness. Further, higher CPC levels predicted greater improvements in usual and rapid gait speed over 1 year.

Conclusions. Baseline CPC levels are associated not only with baseline mobility but also with future physical function, including changes in gait speed. These findings suggest that CPC measurement may be useful as a marker of both current and future physiologic aging and functional decline.

Key Words: Endothelial progenitor cells—Physical performance—Physical function—Aging—Progenitor cells biology

The observation that primitive endothelial (1) and other (2) progenitor cells are present in the circulation fostered great interest in the balance between chronic injury, reparative capacity, and processes such as aging, physical function, and clinical outcomes. We (3) and others (4,5) have proposed that chronic and repetitive cellular injury may lead to progenitor cell exhaustion (3). The loss of reparative capability and diminished functional reserve occur commonly with aging leading to impairment in physical function, yet to date the mechanisms underlying this decline are incompletely understood. Recent research has suggested that circulating progenitor cells (CPCs) may serve as markers of reparative capacity. CPCs are depleted in the elderly individuals (6–9) and are associated with factors that predispose to vascular injury (10,11) and with the degree of vascular injury/disease present at the time of CPC measurement (7,12,13).

Although different markers have been used to define CPCs (2,10,14), CD34, the original marker used to select endothelial progenitor cells, CD133, and ALDH activity (a marker or multiple stem cell phenotypes) (15,16) have been found by our laboratory (7,8,17) and others (18) to best identify CPCs predictive of clinical deterioration.

The Enhancing Fitness in Older Overweight Veterans with Impaired Glucose Tolerance (Enhanced Fitness) trial was a randomized controlled trial testing the effects of a 1-year home-based physical activity telephone counseling intervention compared with usual care on glycemic control (19,20). As part of this study, patients underwent extensive assessments of physical function over the course of follow-up. We wanted to determine the association between CPCs of various phenotypes with physical function as measured by a variety of parameters in a group of patients with mildly decreased physical capacity and impaired glucose tolerance, a stimulus to chronic vascular injury. In a previous publication, we have demonstrated that $CD34^+$, $CD133^+$, CD34/CD133 double-positive, and $ALDH^{br}$ CPCs in particular are associated, cross-sectionally, with mobility and aerobic measures of physical function, suggesting that low CPC levels could be considered markers of diminished physical functioning (3). Yet, there remains limited understanding of whether CPC levels are associated with *future* measures of physical function. We thus undertook the current exploratory analysis to determine the robustness of baseline CPC levels as a predictor of future physical function and whether baseline CPCs—reflecting reparative capacity and ability of the organism to resist future injuries—predict change in physical function over time.

Methods

Enhanced Fitness Study

The Enhancing Fitness in Older Overweight Veterans with Impaired Glucose Tolerance (Enhanced Fitness) trial was a randomized controlled trial testing the effects of a 1-year home-based physical activity telephone counseling intervention compared with usual care on glycemic control (19,20). Enhanced Fitness randomized 302 patients with impaired glucose tolerance (fasting glucose 100–125 mg/dL) but not diabetes into a 1-year physical activity counseling trial. Individuals who exceeded current physical activity recommendations were excluded (21). Outcomes were assessed by individuals blinded to intervention status.

The research protocol was reviewed and approved annually by the institutional review boards of the Durham Veterans Affairs Medical Center and the Duke University Medical Center. Institutional review board approval for this substudy was obtained in August 2009, after which 137 of 138 enrollees consented to participate. Twenty participants were excluded: eight because sufficient blood for analysis was either not obtained or technical issues prevented CPC analysis; three who died during follow-up; and nine in whom follow-up assessments of physical functioning were not completed (3).

Baseline Factors

Demographic and biometric characteristics, including assessment of body mass index, glycemic control, lipids, and inflammatory markers including IL-6, were collected at baseline (20). Comorbidity was assessed using the Older Americans Resources & Services (OARS) Comorbidity and Symptom Index by trained researchers following rigorous, validated survey methods (22). For this, each individual provided a positive or negative response to the question "Do you have any of the following illnesses or conditions at the present time" for 35 unique conditions or symptoms. They also provided a single-item self-report of perceived general health at time of study entry (23).

Physical Function Measures

Physical function was assessed by objective measures of physical performance and self-report of health-related physical function at baseline, 3 months, and 12 months (20). Usual and rapid gait speeds were measured over 2.4 meters with a wireless timing device with the better of two trials recorded. The 6-minute walk test was performed with participants instructed to cover as much distance as they could over 6 minutes. Tests of time to complete five chair stands were performed as described by Guralnik and colleagues (24). Grip strength was measured as the best of three trials for the preferred hand using a hand-held dynamometer. Self-report of function was obtained as part of a separate computer-assisted telephone interview using the physical function subscale of the Medical Outcomes Study 36-item Short-Form Health Survey (SF-36) (23). Trained individuals blinded to study assignment performed each test following standardized and validated methods.

CPC Analysis

Samples for CPC analysis were obtained from participants instructed to refrain from eating or drinking anything past midnight the evening before their appointment. Blood specimens were procured prior to assessments of physical function.

CPC analysis has been previously described (3), and was performed within 3 hours of sample collection using flow cytometry utilizing CD133-phycoerythrin (Miltenyi Biotec, Auburn, CA) and CD34-fluorescein isothiocyanate (Miltenyi Biotec) to identify CPCs based on expression of the cell surface markers CD34 ($CD34^+$), CD133 ($CD133^+$), or both ($CD34^+CD133^+$ cells). In a separate experiment, cells with high aldehyde dehydrogenase activity ($ALDH^{bright}$ or $ALDH^{br}$) were identified using Aldecount tubes (Aldagen, Durham, NC) (3,7), as previously described. Flow cytometry was performed by trained technicians blinded to patient identity. CPCs are reported as percentages of the mononuclear cell population.

Analytical Methods

A statistical approach similar to the baseline analysis (3) was adopted to address the objectives of assessing baseline CPCs with future functional measures. Briefly, CPCs are expressed as a percentage of the total mononuclear cell population. Associations between CPC levels and physical function outcomes were processed using standardized z scores of log-transformed CPC concentrations. The associations of standardized CPCs with the functional outcomes (usual and rapid gait speed, 6-minute walk, chair stands, and the SF-36 physical function subscale) were assessed using ordinary least squares regression in a two-step modeling strategy. The first step estimated the unadjusted association for each functional outcome (dependent variable) and each standardized CPC (independent variable). In the second step, adjusted ordinary least squares models added a set of a priori selected covariates (participant age, body mass index, IL-6 level,

Table 1. Baseline Characteristics of Participants in Longitudinal Analysis (n = 117)

	Participants	Range
Age, mean (*SD*), y	66.7 (6.2)	60–81
Age ≥75 years, no. (%), y	19 (16.2%)	
White race, no. (%)	82 (70.1%)	
Male sex, no. (%)	115 (98.3%)	
Some college education or trade school, no. (%)	69 (59.0%)	
Arthritis, no. (%)	57 (48.7%)	
Stroke, no. (%)	2 (1.7%)	
Heart disease, no. (%)	33 (28.2%)	
Circulation trouble in arms or legs, no. (%)	15 (12.8%)	
Anemia, no. (%)	2 (1.7%)	
High blood pressure, no. (%)	82 (70.1%)	
Emphysema or COPD, no. (%)	13 (11.1%)	
Kidney disease, no. (%)	1 (0.9%)	
Health quality of life		
General health, mean (*SD*), range 0–100	66.3 (18.5)	10–100
Number of comorbidities, mean (*SD*)	3.60 (2.33)	0–10
Number of symptoms, mean (*SD*)	1.97 (1.56)	0–6
Anthropometric and biochemical, mean (*SD*)		
BMI, kg/m^2	31.4 (3.7)	24.9–42.1
Insulin, μIU/mL	10.53 (5.79)	1–29
Hemoglobin A1c, %	5.87 (0.43)	4–6.6
Glucose (mg/dL)	109.65 (7.17)	100–125
Cholesterol, mg/dL	175.4 (30.2)	110–248
Triglycerides, mg/dL	139.0 (73.3)	33–530
HDL, mg/dL	38.0 (9.2)	21–68
LDL, mg/dL	109.7 (27.6)	51–170
HOMA-IR	1.44 (0.81)	0.12–3.75
Physical performance,* mean (*SD*)		
Gait speed: usual pace, m/s	1.26 (0.22)	0.60–1.72
Gait speed: rapid, m/s	1.88 (0.38)	0.74–2.71
6-min walk distance, yd	578.0 (118.5)	130–872
Chair stands, total s	11.2 (3.4)	5–27
Balance time, s	9.40 (1.83)	1–10
Grip strength, kg	35.4 (7.6)	16–54
SPPB summary score, range 4–12	11.1 (1.4)	4–12
Self-reported function, mean (*SD*)		
Physical function, range 0–100	78.9 (18.6)	30–100

Notes: BMI = body mass index; COPD = chronic obstructive pulmonary disease; HDL = high-density lipoprotein; HOMA-IR = homeostasis model of assessment-insulin resistance; LDL = low-density lipoprotein; *SD* = standard deviation; SPPB = Short Physical Performance Battery.

*Gait speeds are speeds measured walking at usual (usual) pace and as rapidly as possible (rapid). Six-minute walk distance is distance walked in 6 minutes. Chair stand is the time required to complete five chair stands (better fitness associated with lower value). Balance time is the time (up to 10 seconds) for which a patient could stand in one of the three hierarchical positions as outlined (24). Grip strength is force generated using a hand-held dynamometer. Better fitness is represented by higher values. The SPPB summary score is developed by grading performance on usual walking speed, time for five chair stands, and balance test according to quartiles in the Established Populations for the Epidemiologic Study of the Elderly (24), thus each patient gets a score of 1–4 for each assessment.

and self-reported presence of arthritis, effects of stroke, circulation problems, anemia, and high blood pressure) as independent variables. In these regression models, parameter estimates reflect the association of standardized CPC level with functional measures so that the parameter estimate is the magnitude of change of the functional measure with a 1 *SD* increase in CPC level. Presented are parameter estimates (Est.) and standard errors (*SE*) for these estimates. In addition, collinearity diagnostics were assessed among the covariates to determine whether collinearity was a significant factor in the results.

The association of baseline CPC levels with change of functional measures from baseline were analyzed using a mixed-model analysis of variance procedure using maximum likelihood estimation. This method allows for estimation in the presence of missing values. All individuals with at least one follow-up were included in the mixed-model analyses. As with the serial cross-sectional analyses, two sets of models were conducted. In the unadjusted models, only baseline values of the functional measures and indicators for the 3- and 12-month assessments were included as independent variables, with the dependent variable being the assessed functional measure value at 3 and 12 months. In the adjusted analysis, the same set of covariates as before was included as predictor variables (age, treatment arm, body mass index, comorbid conditions, and IL-6 level).

Statistical significance was declared at $p < .05$. Given the exploratory nature of the aims of this study, no adjustments were made for multiple comparisons. All analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, NC).

Table 2. Measures of Physical Function Over Time

	Baseline		3 months		12 months	
	Mean (*SD*)	Min–Max	Mean (*SD*)	Min–Max	Mean (*SD*)	Min–Max
Usual gait speed (m/s)	1.25 (0.22)	0.60–1.72	1.29 (0.25)	0.70–1.97	1.27 (0.25)	0.49–1.81
Rapid gait speed (m/s)	1.87 (0.39)	0.74–2.71	1.86 (0.39)	0.83–2.87	1.86 (0.41)	0.59–2.87
6-min walk distance (ft)	1717 (359)	391–2616	1813 (353)	771–2715	1823 (363)	762–2658
SF-36 physical function score	77.89 (19.12)	25–100	77.91 (22.17)	10–100	76.17 (23.26)	10–100
Time for five chair stands (s)	11.32 (3.45)	5.0–27.0	11.08 (3.37)	6.6–25.0	10.97 (4.44)	5.2–41.6

Note: SD = standard deviation.

Results

The clinical characteristics of the CPC cohort (Table 1) mirror those of the overall Enhanced Fitness cohort (20), as did measures of physical performance. Patients ranged in age from 60 to 81 years, mean age 66.7, and were almost exclusively men (98%). Participants averaged 3.6 comorbidities with arthritis, heart disease, circulation problems, and high blood pressure reported as most prevalent. Baseline physical performance and self-reported function were at, or slightly lower than, age-based norms (25,26).

Physical Function Over Time in the CPC Cohort

Means and ranges of physical function measures over the course of the study in the CPC cohort are shown in Table 2. It must be noted that there was no change in physical performance over time or treatment effect of the intervention in the parent study. We limited our analysis to those measures of physical function (usual and rapid gate speed, distance walked in 6 minutes, time to complete five chair stands, and SPF-36 physical function performance score) that were associated with CPC levels at baseline (3).

Baseline CPCs Predict Future Physical Function

We evaluated the association of baseline $CD34^+$, $CD133^+$, $CD34^+CD133^+$, and $ALDH^{br}$ cells with measures of future physical function at the 3- and 12-month time points (Tables 3 and 4). Higher numbers of each of these CPCs were positively associated with future levels of mobility and aerobic physical functioning, including usual and rapid gait speed as well as 6-minute walk distance at 3 months. These observations remained significant after adjustment for treatment arm, age, body mass index, self-reported conditions associated with impairments in physical function (including arthritis, effects of stroke, circulation problems, anemia, and high blood pressure), and IL-6, a marker of inflammation (Table 3). Baseline CPC numbers were not associated with future SF-36 functional score or time to complete five chair stands. In addition, collinearity diagnostics among the covariates determined that this was not a significant factor in the results.

These observations were replicated when association with 12-month measures of physical functioning was tested, although $ALDH^{br}$ cell numbers were associated in a statistically significant level only with rapid gait speed (Table 4).

Baseline CPCs Predict Change in Physical Function Over Time

We next assessed whether CPC levels predict changes in physical function over the time period of observation. CPCs defined on the basis of cell surface markers ($CD34^+$, $CD133^+$, and $CD34^+CD133^+$) were each tightly associated with changes in usual gait speed and rapid gait speed over time (Table 5)—associations that again remained robust after adjustment for factors stated previously. The association with $ALDH^{br}$ cells was weaker. Changes in 6-minute walk distance, as well as SF-36 physical functioning scores and chair stands, were not associated in a statistically significant manner with levels of any of the CPCs analyzed.

Discussion

Association of CPCs and Physical Function

Our current study demonstrates that baseline CPCs have implications for a patient's ability to maintain physical function over a year, suggesting that higher CPC levels may be associated with maintenance of future physical independence.

One explanation for this association is that CPCs are reflective of current physical function, which in turn is highly predictive of future physical function. If patients had minimal or uniform changes in physical function over time, the association observed at baseline would be replicated at future time points. In this model, however, there would be minimal to no correlation between CPCs and change in physical function.

We therefore directly tested this hypothesis (Table 5) and found that CPCs predict not only future function, but change in function over time, with higher CPC levels predicting greater improvement in both usual and rapid walking speed over a full year of follow-up. This analysis supports the hypothesis that CPCs (as measurements of reparative capacity) reflect the organism's ability to continue to resist ongoing injury and maintain physical function over time.

A Gerontological Model of Stem Cell–Mediated Repair and Functional Impairment

We have previously postulated that the loss of reparative capacity is a fundamental biological process that may be a vital component to determining the organism's ability to maintain healthy homeostasis. Physical health and physiologic functioning are determined by a balance between the rate of chronic injury due to biological, environmental, and physical injury and the ability to effect biological repair. Low levels of CPCs represent exhaustion of a finite capacity for stem cell–mediated repair leading to overt clinical disease and loss of function (4). In this model, lower reparative capacity would precede and predict loss of future physical capabilities and perhaps risk of frailty and disease.

A significant limitation of our previous cross-sectional study was the inability to infer a temporal relationship between CPCs and loss

Table 3. Association of Baseline CPC Types With 3-month Assessments of Physical Function

	$CD34^+$				$CD133^+$				$CD34^+CD133^+$				$ALDH^{br}$			
	Unadjusted		Adjusted*		Unadjusted		Adjusted*		Unadjusted		Adjusted*		Unadjusted		Adjusted*	
	Est (*SE*)	*p* Value	Est (*SE*)	*p* Value	Est (*SE*)	*p* Value	Est (*SE*)	*p* Value	Est (*SE*)	*p* Value	Est (*SE*)	*p* Value	Est (*SE*)	*p* Value	Est (*SE*)	*p* Value
Usual gait speed (m/s)	0.073 (0.023)	.002	0.065 (0.022)	.003	0.068 (0.025)	.006	0.071 (0.022)	.002	0.088 (0.024)	.0003	0.084 (0.022)	.0003	0.064 (0.023)	.007	0.060 (0.022)	.008
Rapid gait speed (m/s)	0.101 (0.036)	.006	0.086 (0.034)	.014	0.086 (0.038)	.027	0.089 (0.036)	.015	0.102 (0.038)	.009	0.089 (0.036)	.016	0.106 (0.036)	.004	0.080 (0.035)	.012
6-min walk distance (ft)	74.4 (33.1)	.027	59.6 (28.0)	.036	52.2 (35.2)	.14	56.8 (29.4)	.056	70.6 (34.6)	.044	59.8 (29.5)	.045	68.8 (33.0)	.039	55.4 (28.9)	.058
SF-36 physical function score	3.02 (2.05)	.144	1.57 (1.92)	.42	3.01 (2.16)	.17	2.73 (1.99)	.17	2.81 (2.16)	.19	1.77 (2.04)	.39	2.39 (2.08)	.25	0.77 (1.99)	.70
Time for five chair stands (s)	−0.56 (0.32)	.086	−0.37 (0.32)	.25	−0.40 (0.34)	.24	−0.36 (0.34)	.28	−0.47 (0.34)	.17	−0.31 (0.34)	.37	−0.67 (0.33)	.041	−0.49 (0.33)	.14

Notes: CPC = circulating progenitor cell; Est = parameter estimate; *SE* = standard error of parameter estimate.
*Adjusted for age, arm, body mass index, comorbid conditions, and IL-6 level.

Table 4. Association of Baseline CPC Types With 12-Month Assessments of Physical Function

	$CD34^+$				$CD133^+$				$CD34^+CD133^+$				$ALDH^{br}$			
	Unadjusted		Adjusted*		Unadjusted		Adjusted*		Unadjusted		Adjusted*		Unadjusted		Adjusted*	
	Est (*SE*)	*p* Value	Est (*SE*)	*p* Value	Est (*SE*)	*p* Value	Est (*SE*)	*p* Value	Est (*SE*)	*p* Value	Est (*SE*)	*p* Value	Est (*SE*)	*p* Value	Est (*SE*)	*p* Value
Usual gait speed (m/s)	0.057 (0.026)	.032	0.041 (0.024)	.087	0.057 (0.027)	.035	0.052 (0.024)	.033	0.067 (0.028)	.018	0.055 (0.025)	.031	0.028 (0.027)	.30	0.028 (0.025)	.26
Rapid gait speed (m/s)	0.141 (0.042)	.001	0.126 (0.042)	.003	0.109 (0.044)	.016	0.111 (0.043)	.011	0.147 (0.046)	.002	0.137 (0.044)	.003	0.106 (0.044)	.018	0.109 (0.043)	.013
6-min walk distance (ft)	100.3 (38.8)	.023	70.1 (31.2)	.028	106.6 (40.4)	.019	89.1 (30.6)	.005	86.0 (41.6)	.069	77.8 (33.4)	.023	61.6 (38.2)	.15	47.8 (31.6)	.14
SF-36 physical function score	4.56 (2.31)	.051	3.28 (2.20)	.14	3.43 (2.42)	.916	3.54 (2.22)	.12	2.33 (2.50)	.35	2.04 (2.37)	.39	3.26 (2.30)	.16	1.30 (2.27)	.57
Time for five chair stands (s)	−0.71 (0.35)	.047	−0.53 (0.35)	.136	−0.76 (0.36)	.036	−0.67 (0.35)	.057	−0.68 (0.37)	.07	−0.56 (0.37)	.14	−0.56 (0.35)	.11	−0.36 (0.36)	.32

Notes: CPC = circulating progenitor cell; Est = parameter estimate; *SE* = standard error of parameter estimate.
*Adjusted for age, arm, body mass index, comorbid conditions, and IL-6 level.

Table 5. Association of Baseline CPCs (standardized) With Trajectories of Change (3- and 12-month Assessments) of Functional Measures

	$CD34^+$				$CD133^+$				$CD34^+CD133^+$				$ALDH^{br}$			
	Unadjusted		Adjusted*		Unadjusted		Adjusted*		Unadjusted		Adjusted*		Unadjusted		Adjusted*	
	Est	*p* Value	Est	*p* Value	Est	*p* Value	Est	*p* Value	Est	*p* Value	Est	*p* Value	Est	*p* Value	Est	*p* Value
Usual gait speed (m/s)	0.026	.035	0.025	.034	0.027	.033	0.029	.019	0.033	.010	0.034	.007	0.009	.467	0.011	.388
Rapid gait speed (m/s)	0.056	.007	0.056	.006	0.052	.013	0.057	.007	0.059	.007	0.061	.005	0.042	.041	0.050	.018
6-min walk distance (ft)	4.29	.774	14.02	.228	18.22	.233	17.84	.136	1.56	.920	16.41	.182	–17.7	.229	2.07	.860
SF-36 physical function score	1.50	.229	1.13	.364	1.90	.143	2.18	.088	0.963	.463	0.780	.554	0.825	.508	–0.052	.967
Time for five chair stands (s)	–0.07	.559	–0.04	.744	–0.052	.689	-0.003	.983	0.078	.556	0.108	.416	0.075	.551	0.097	.449

Notes: CPC = circulating progenitor cell; Est = parameter estimate.
*Adjusted for age, arm, body mass index, comorbid conditions, and IL-6 level.

of physical function. We now demonstrate that CPCs at baseline predict both absolute levels of physical functioning and change in physical function over time for mobility-related functions.

The importance of CPC-mediated repair is reflected when comparing the association of baseline CPCs with measures of physical function at various time points. Parameter estimates for the association between baseline CPCs and measures of usual and rapid gait speed are uniformly higher at 3 and 12 months compared with baseline. This observation reflects the association of CPCs with future changes in physical function, implying that patients with poorer reparative capacity will continue to lose physical function over time, and predicts a continued divergence in the levels of physical function between those with lower or higher CPC numbers.

Understanding the Balance Between Injury and Repair

Our findings imply that biological repair mechanisms play an important independent role in maintenance of physical functioning. Our understanding of and ability to measure ongoing injury are limited to indirect markers such as cardiovascular risk factors and serum factors, such as IL-6. Our adjusted analysis suggests that CPC levels remain predictive of future physical function independent of these measures of ongoing injury and that reparative capacity is an important component to incorporate into a model that predicts future outcomes.

To limit multiple testing, we focused our analysis on CPCs and outcomes that were associated cross-sectionally at baseline: cells that are angiogenic/hematopoietic in nature and are related to measures of cardiovascular/mobility/locomotor functional outcomes. The robust associations we observe with these cells are undoubtedly influenced by multiple factors, including the robustness of expression of these markers, making enumeration of these cell types more reproducible and accurate. It is notable that other assessments of physical function, such as grip strength and balance time, did not associate with CPCs at baseline. Whether measures such as grip strength are more associated with different reparative mechanisms/cell types, perhaps myoprogenitors, is an interesting area of exploration.

Interventions to Improve Outcomes

Our observations suggest that interventions targeted toward augmentation of progenitor cell–mediated repair might prove powerful approaches in preventing decline or improving physical function over time and in reducing disability. These findings are particularly relevant given that participants in the Enhanced Fitness study were functionally healthy community dwellers who would not be considered physically impaired, suggesting that CPC measurement identifies patients at higher risk of future loss of mobility-related physical functioning prior to the onset of significant physical impairment (3).

Exercise interventions mobilize CPCs in a variety of clinical settings (27–30), although these studies measure the effect over a short interval. It is tempting to speculate that some of the benefit of exercise is mediated by CPC mobilization (31,32). Pharmacologic measures such as statin therapy offer an alternative approach (33–35). It may be that the immense clinical benefit of this class of drugs is at least in part secondary to improvements in reparative capacity due to stem cell mobilization, although other agents that increase CPCs have not had similar effects on clinical outcomes (36–41).

Given that the loss of physical function over time observed in patients with CPC depletion is closely related to such events as incident hospitalization, falls, and death, our results indicate that the relationship between stem cell–mediated repair, aging, and loss of physical functioning merits significant attention and research.

Limitations

Our results are observational and do not prove a direct mechanism of action of CPCs on biological aging; however, the association with both baseline and future measures of physical assessments as well as with the change in physical function over time substantiates the role of CPCs in the aging process and suggests a temporal relationship where low levels of CPCs precede loss of physical function.

We measured CPCs at a single time point, so we cannot determine whether the lower numbers of CPCs that predict future events are due to depletion of an originally more robust stem cell pool or to interpatient variability in CPC numbers due to genetic or other factors.

Our patients were almost exclusively men, reflective of our VA population. The results may not be applicable to a more representative population.

Conclusions

Our findings support the utility of CPC measurement as a marker of general reparative capacity with prognostic implications for future physical functioning. These observations suggest that CPC levels reflect the organism's ability to maintain physical capacity and resist ongoing injury and may be important predictors of longer-term outcomes. If verified in other settings, this observation would add to the growing body of evidence that progenitor cell–mediated repair is a potential mechanistic explanation for resiliency and biological aging.

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