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Functional Decline in Patients With and Without Peripheral Arterial Disease: Predictive Value of Annual Changes in Levels of C-Reactive Protein and D-Dimer

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Background. Inflammation may be a potential mechanism of aging-related functional decline. We determined whether greater annual increases in levels of high sensitivity C-reactive protein (hsCRP) and D-dimer predicted greater decline in functioning among persons with and without lower extremity peripheral arterial disease (PAD).

Methods. We prospectively studied 296 men and women with PAD and 191 without PAD. Objective measures of functioning, hsCRP, and D-dimer were obtained at baseline and annually for 3 years (mean follow-up = 36.3 ± 6.4 months).

Results. Among PAD participants, greater annual increases in hsCRP were associated with greater annual declines in 6-minute walk performance (–2.63 ft/mg/L, $p = .039$) but not in other functional outcomes. Higher prior year absolute hsCRP levels were associated with greater declines in 6-minute walk (–2.93 ft/mg/L, $p = .022$), summary performance score (–0.038/mg/L, $p = .017$), and rapid paced 4-meter walk (–0.29 cm/s/mg/L, $p = .026$) during the subsequent year. Among participants without PAD, greater annual increases in hsCRP were associated with greater annual declines in 6-minute walk (–7.47 ft/mg/L, $p = .002$), usual-pace 4-meter walk (–0.33 cm/s/mg/L, $p < .001$), fast paced 4-meter walk (–0.56 cm/s/mg/L, $p = .003$), and the summary performance score (–0.029 mg/L, $p < .001$). There were no consistent associations between D-dimer levels and functional decline.

Conclusion. These findings suggest that inflammation may play a role in functional decline in persons with and without PAD.

INFLAMMATION is a potential mediator of aging-related functional decline (1–3). Inflammatory cytokines may alter muscle homeostasis by inhibiting skeletal muscle repair after injury, promoting muscle proteolysis, and impairing strength (4–7). In older healthy populations, elevated inflammatory factor levels are associated with reduced muscle mass, reduced strength, and increased functional decline (7–9). Patients with lower extremity peripheral arterial disease (PAD) have increased inflammatory marker levels and greater functional decline than do persons without PAD (10,11). However, the contribution of inflammation to functional decline in PAD is not fully understood.

Previous studies of older adults show that elevated levels of inflammatory markers are more predictive of near-term than later-term cardiovascular events (12,13). One potential explanation for this phenomenon is that increases in inflammatory or thrombotic marker levels may acutely increase cardiovascular risk. In a similar manner, increases in inflammatory and thrombotic marker levels may promote functional decline, perhaps because of an acutely detrimental effect on skeletal muscle function. However, temporal associations between changing levels of inflammatory factors with functional decline in persons with and without PAD are unknown.

We previously demonstrated significant associations between higher levels of high sensitivity C-reactive protein (hsCRP) and D-dimer with greater impairment in lower extremity functioning in persons with and without PAD (14,15). In the present report, we describe associations between changes in hsCRP and D-dimer with functional decline in the same cohort of persons with and without PAD. To determine the relative associations between change versus absolute levels of these blood factors with functional decline, we also studied associations between prior year hsCRP and D-dimer levels with functional decline during the subsequent year. We hypothesized that functional decline would be greater in patients with annually increasing hsCRP or D-dimer compared to those with constant or declining levels of hsCRP or D-dimer. We hypothesized that higher absolute levels of hsCRP or D-dimer in a given year would be associated with greater functional decline during the subsequent year.

Methods

Study Overview

The protocol was Institutional Review Board-approved by Northwestern University's Feinberg School of Medicine

and Catholic Health Partners Hospitals. Participants gave written informed consent. This study was performed as part of a longitudinal observational study designed to identify characteristics associated with lower extremity functional decline in persons with and without PAD. Study aims included determining whether annual levels of hsCRP and D-dimer and annual changes in hsCRP and D-dimer levels were associated with increased rates of functional decline.

Participant Identification

PAD participants and half of the non-PAD participants were identified consecutively from among patients undergoing lower extremity arterial testing in three Chicago-area noninvasive vascular laboratories. Recruiting PAD participants from a vascular laboratory helped ensure that our cohort would include PAD participants with a full spectrum of PAD severity. Remaining non-PAD participants were identified consecutively from among patients with appointments in a large general medicine practice. All participants were 55 years old or older at baseline. Participants attended a baseline visit and three annual follow-up visits. For each of the three follow-up visits, we aimed for participants to return between 10 and 14 months after the anniversary of their baseline study visit.

Exclusion Criteria

PAD was defined as an ankle brachial index (ABI) $<$ 0.90 (16). Individuals with ABI $>$ 1.50 were excluded (17). Demented patients, nursing home residents, wheelchair-bound patients, and patients with foot or leg amputations were excluded (10). Non-English-speaking patients were excluded because investigators were not fluent in non-English languages. Patients with recent major surgery were excluded. Persons with a normal ABI and prior lower extremity revascularization at baseline were excluded, because they could not clearly be classified as PAD or non-PAD. Participants who underwent lower extremity revascularization after baseline were excluded after their revascularization date, because revascularization may affect the natural history of functional decline.

ABI Measurement

Systolic pressures in both brachial, dorsalis pedis, and posterior tibial arteries were measured twice with a handheld Doppler probe (Nicolet Vascular Pocket-Dop II; Golden, CO). The ABI was calculated in each leg by dividing average pressures in each leg by the average of the four brachial pressures (18). Average brachial pressures in the arm with highest pressure were used when one brachial pressure was higher than the opposite brachial pressure in both measurement sets, and the two brachial pressures differed by $\geq$10 mmHg in at least one measurement set, because in such cases subclavian stenosis was possible (19). Lowest leg ABI was used in analyses.

Comorbidities

Algorithms developed for the Women's Health and Aging Study were used to document comorbidities at baseline (20). These algorithms combine data from patient report, physical examination, medical record review, medications, laboratory values, and a primary care physician questionnaire. Comorbidities assessed were angina, diabetes mellitus, myocardial infarction, stroke, heart failure, pulmonary disease, spinal stenosis, disk disease, and cancer. Criteria developed by the American College of Rheumatology were used to diagnose knee and hip osteoarthritis (21,22).

Functional Measures

Functional measures were performed at baseline and at each follow-up visit.

Six-minute walk.—Following a standardized protocol (23,24), participants walked up and down a 100-foot hallway for 6 minutes after instructions to cover as much distance as possible.

Repeated chair rises.—Participants sat in a straight-backed chair with arms folded across their chest and stood five times consecutively as quickly as possible. Time to complete five chair rises was measured (25,26).

Standing balance.—Participants were asked to hold three standing positions for 10 seconds each: standing with both feet together side-by-side and parallel (side-by-side stand), standing with feet parallel with the toes of one foot adjacent to and touching the heel of the opposite foot (semi-tandem stand), and standing with one foot directly in front of the other (tandem stand) (25,26).

Four-meter walking velocity.—Walking velocity was measured with a 4-meter walk performed at usual and fastest pace. Each walk was performed twice. The faster walk in each pair was used in analyses (25,26).

Summary performance score.—The summary performance score is a global measure of lower extremity functioning that predicts mobility loss, nursing home placement, and mortality among older men and women (25,26). A 0–4 score is assigned for performance on usual-paced 4-meter walking velocity, repeated chair rises, and standing balance, respectively. Individuals receive a 0 for each task they are unable to complete. One to four scores for each task are assigned based on quartiles of performance for community-dwelling men and women. Scores are summed to obtain the summary performance score (range 0–12).

D-Dimer Levels

An Asserachrom D-Di kit (Diagnostica Stago, Asnieres-Sur-Seine, France) was used to measure fibrin D-dimer quantitatively using an enzyme-linked immunosorbent assay (ELISA) procedure.

hsCRP Levels

hsCRP levels were determined using an immunotechnique on the Behring BN II analyzer (Dade Behring, Wilmington, DE).

Other Measures

Height and weight were measured at each visit. Pack-years of cigarette smoking were determined by using patient report.

Table 1. Characteristics of Participants According to Presence Versus Absence of PAD at Baseline

Participant Characteristics	PAD ABI < 0.90 (*N* = 296)	No PAD ABI 0.90–1.50 (*N* = 191)	All Participants (*N* = 487)
Age, y*	71.4 (8.4)	69.4 (7.9)	70.6 (8.3)
Male, %*	64.5	52.4	59.8
African American, %	11.8	17.8	14.2
Ankle brachial index†	0.659 (0.14)	1.11 (0.11)	0.836 (0.26)
Cigarette smoking, pack-years†	38.9 (34.4)	16.9 (26.4)	30.3 (33.3)
Body mass index, kg/m^2	27.2 (4.8)	28.2 (5.3)	27.6 (5.0)
Diabetes, %†	32.1	17.8	26.5
Cardiac or cerebrovascular disease, %†	58.1	34.0	48.7

Notes: Values are expressed as mean (standard deviation) unless otherwise indicated. Cardiac or cerebrovascular disease was defined as one or more of the following: history of myocardial infarction, heart failure, angina, and stroke.

*$p < .01$, †$p < .001$, for comparisons between participants with and without PAD.

PAD = Peripheral arterial disease; ABI = ankle brachial index.

Follow-Up

Individuals unable to complete functional measures due to wheelchair confinement, shortness of breath, or other significant symptoms were classified as too disabled to complete functional measures. When no data were available because a participant refused to walk, a priori criteria were used to determine whether that participant was likely to have been too disabled to walk (10). Participants who did not complete functional assessments and met at least two of the following criteria were considered too disabled to walk: (a) participant reported walking fewer than 5 blocks during the previous week; (b) score for repeated chair rises equaled 0 or 1; or (c) score for the standing balance test equaled 0 or 1 (10). Participants classified as too disabled to complete functional assessments were assigned the poorest performance among those completing testing at the corresponding visit.

Statistical Analyses

Baseline characteristics between participants with and without PAD were compared using general linear models for continuous variables and chi-square tests for categorical variables. In comparing change in functional decline across different patient groups, a longitudinal or repeated-measures analysis of covariance was carried out using a linear mixed effect model approach with compound symmetry as the covariance structure (27). The dependent variable was the successive annual difference in functional performance (i.e., the 6-minute walk test) in a repeated-measures model (10). Baseline covariates were age, sex, race, and comorbidities. Time-dependent covariates were body mass index, pack-years of cigarette smoking, statin use (for hsCRP analyses), prior year ABI, prior year performance, and annual change in ABI. Dummy variables indicating different visits were also included in analyses. To determine relative associations between annual change in blood factor level (i.e., hsCRP) with functional decline and the absolute hsCRP level with functional decline, both variables were included in the model. Adjusting for the absolute hsCRP level during the prior year also allowed us to control the magnitude of hsCRP change for the amount of inflammation in the prior year. For analyses performed among PAD participants only, baseline leg symptoms were also an independent variable (10).

Handling missing data.—Under this initial linear mixed effect model, statistically valid inference is guaranteed provided missing data caused by patient dropout is unrelated to unobserved data (i.e., any missing data are missing at random). As a safeguard against violations to this assumption that missing data are missing at random, we repeated the fully adjusted comparisons of functional performance between groups using a repeated-measures pattern-mixture analysis of covariance model (28,29). In this model, different patterns of missing data are included as binary indicator covariates. By including patterns of missing data in analyses as centered covariates and averaging over these patterns using adjusted least squares means, one can obtain an unbiased estimate of the marginal means (29). Analyses were performed using SAS statistical software (version 9.1; SAS Institute Inc., Cary, NC).

Results

Table 1 shows baseline characteristics of participants. PAD participants were older and included a higher proportion of males and patients with diabetes and cardiac or cerebrovascular disease than did participants without PAD. PAD participants had more pack-years of cigarette smoking than did individuals without PAD.

Of 363 eligible PAD participants who completed baseline testing, 296 (81.5%) completed the first follow-up visit including phlebotomy. Of 221 eligible non-PAD participants who completed baseline testing, 191 (86.4%) completed the first follow-up visit and were included in analyses. Of the 97 (67 PAD and 30 non-PAD) participants who did not complete follow-up testing, 12 of the PAD and 4 of the non-PAD participants died between their baseline and first follow-up visits.

Baseline hsCRP levels were higher among PAD than among non-PAD participants (Table 2). Between baseline and the third follow-up visit, mean hsCRP levels increased to a greater degree among non-PAD than among PAD participants (Table 2). D-dimer levels were higher at baseline and increased to a greater degree during follow-up among PAD participants. These findings did not change significantly when analyses were repeated among participants who attended all follow-up visits (data not shown).

Tests for interactions between presence versus absence of PAD and the association between change in hsCRP and functional decline were statistically significant or nearly significant for each outcome: 6-minute walk, $p = .059$; usual pace 4-meter walk, $p = .001$; fast paced 4-meter walk, $p = .042$; summary performance score, $p = .090$. Remaining analyses were performed separately in participants with and without PAD, respectively.

Table 3 shows associations between (a) annual change in hsCRP levels and annual functional decline and (b) prior

Table 2. Blood Factor Levels and Functional Outcomes According to Presence Versus Absence of Peripheral Arterial Disease (PAD)*

Baseline, Follow-Up and Mean Change in Blood Factor Levels and Functional Performance	PAD ABI < 0.90 ($N = 296$)	No PAD ABI 0.90–1.50 ($N = 191$)	All Participants ($N = 487$)
Baseline hsCRP, mg/L	4.7 (5.5)	4.3 (5.4)	4.5 (5.5)
FV-1 hsCRP, mg/L	4.3 (8.0)	3.3 (4.9)	3.9 (6.9)
FV-2 hsCRP, mg/L	5.7 (11.7)	4.3 (6.1)	5.1 (9.8)
FV3 hsCRP, mg/L	5.4 (8.7)	5.1 (12.2)	5.3 (10.3)
Mean change in hsCRP (FV3 − baseline visit values), mg/L*	0.19 (10.0)	0.68 (11.6)	0.4 (10.7)
Baseline D-dimer, ug/ml†	0.93 (1.02)	0.55 (0.33)	0.78 (0.84)
FV-1 D-dimer, μg/ml†	0.88 (1.09)	0.56 (0.37)	0.75 (0.89)
FV-2 D-dimer, μg/ml†	0.92 (1.02)	0.52 (0.35)	0.75 (0.84)
FV-3 D-dimer, μg/ml†	1.09 (1.58)	0.60 (0.43)	0.89 (1.25)
Mean change in D-dimer (FV3 − baseline visit values), μg/ml*,¶¶	0.21 (1.04)	0.04 (0.33)	0.13 (0.82)
Functional outcome measures			
Baseline 6-min walk distance, ft†	1169 (361)	1452 (431)	1279 (413)
Baseline normal pace 4-m walking velocity, cm/s†	90 (21)	96 (20)	92 (21)
Baseline rapid pace 4-m walking velocity, cm/s††	123 (27)	131 (28)	126 (28)
Baseline summary performance score (0–12 score, 12 = best)‡	9.8 (2.3)	10.5 (2.0)	10.1 (2.2)
Mean change in 6-min walk distance (FV3 − baseline)*	−92.2 (286)	−67.0 (333)	−82 (307)
Mean change in normal pace 4-m walking velocity (FV3 − baseline), cm/s*	−4.5 (19)	−4.1 (18)	−4.3 (19)
Mean change in rapid pace 4-m walking velocity (FV3 − baseline), cm/s*	−8.3 (24)	−8.2 (25)	−8.2 (24)
Mean change in summary performance score (FV3 − baseline), 0–12 score, 12 = best*	−0.77 (2.00)	−0.54 (2.16)	−0.67 (2.07)

Notes: Values are expressed as mean (standard deviation) unless otherwise indicated.

*Includes only the subset of participants with data available for analyses at both FV-1 and FV-3.

†$p < .001$; ‡$p < .002$; ††$p < .003$; ¶¶$p < .05$, for comparisons between participants with and without PAD.

PAD = Peripheral arterial disease; ABI = ankle brachial index; hsCRP = high sensitivity C-reactive protein; FV-1 = first annual follow-up visit; FV-2 = second annual follow-up visit; FV-3 = third annual follow-up visit.

year hsCRP levels and functional decline during the subsequent year, adjusting for age, sex, race, prior year performance, comorbidities, prior year ABI, change in ABI, body mass index, cigarette smoking, statin use, patterns of missing data, a dummy variable representing each visit, and leg symptoms (PAD participants only). Among PAD participants, greater increases in hsCRP since the prior year were associated with greater decline in 6-minute walk performance but not other functional outcomes since the prior year. Higher prior year hsCRP levels were associated with significantly greater decline during the subsequent year in 6-minute walk, fast paced 4-meter walking velocity, and the summary performance score.

Among participants without PAD, greater increases in hsCRP since the prior year were associated with significantly greater decline in all functional outcome measures (Table 3). There were no significant associations between prior year hsCRP levels and functional decline during the subsequent year among non-PAD participants.

Analyses were repeated after excluding participants with very high hsCRP levels who had large annual changes in hsCRP. Participants with either (a) hsCRP levels >10 mg/L in any year whose hsCRP changed by 5 mg/L or more in the subsequent year or (b) hsCRP levels <10 mg/L whose hsCRP increased by ≥5 resulting in a level of 10 mg/L in the subsequent year were excluded. After these exclusions, most findings were no longer statistically significant. However, point estimates were similar to those in Table 3, suggesting that excluding these participants reduced our statistical power.

Table 3. Annual Changes in Lower Extremity Functioning According to Standardized Change in hsCRP Over a 3-Year Follow-Up Among Men and Women With and Without PAD ($N = 487$)

	Participants With PAD ($N = 296$)				Participants Without PAD ($N = 191$)			
hsCRP	Annual Rate of hsCRP Change (95% CI)	*p* Value	Prior Year hsCRP, Regression Coefficient (95% CI)	*p* Value	Annual Rate of hsCRP Change (95% CI)	*p* Value	Prior Year hsCRP, Regression Coefficient (95% CI)	*p* Value
6-min walk, ft	−2.63 (−5.12 to −0.14)	.039	−2.93 (−5.43 to −0.44)	.022	−7.47 (−12.2 to −2.75)	.002	−0.026 (−2.68 to 2.63)	.985
Usual pace 4-m walk, cm/s	0.01 (−0.10 to 0.11)	.862	−0.08 (−0.37 to 0.21)	.587	−0.33 (−0.46 to −0.20)	<.001	−0.15 (−0.32 to 0.02)	.084
Fast pace 4-m walk, cm/s	−0.12 (−0.32 to 0.09)	.263	−0.29 (−0.55 to −0.04)	.026	−0.56 (−0.93 to −0.19)	.003	−0.07 (−0.28 to 0.14)	.508
Summary Performance Score	−0.014 (−0.037 to 0.009)	.233	−0.038 (−0.069 to −0.007)	.017	−0.029 (−0.040 to −0.020)	<.001	−0.014 (−0.033 to 0.004)	.132

Notes: Results of mixed linear regression models. Analyses adjusted for age, sex, race, prior year performance, prior year blood factor level, change in ankle brachial index (ABI), prior year ABI, comorbidities, leg symptoms (PAD group only), time-dependent (body mass index, pack-years smoking, statin use), patterns of missing data, and dummy variable for each visit.

CI = confidence interval; hsCRP = high sensitivity C-reactive protein; PAD = peripheral arterial disease.

Among persons with and without PAD, there were no consistent, significant associations between change in D-dimer levels or prior year D-dimer levels with functional decline during the subsequent year (data not shown).

Discussion

Among participants with PAD, greater annual increases in hsCRP levels were associated with greater annual decline in 6-minute walk performance. In addition, higher actual hsCRP levels were associated with significantly greater functional decline during the subsequent year in three of the four functional outcomes. Among participants without PAD, greater increases in hsCRP since the prior year were associated with greater functional decline since the prior year for all functional outcomes. However, actual prior year hsCRP levels were not predictive of functional decline during the subsequent year in persons without PAD. No consistent, significant associations between D-dimer levels and functional decline were observed.

One potential explanation for differences in our findings between PAD and non-PAD participants may be that hsCRP levels started lower and increased to a greater degree during follow-up in non-PAD as compared to PAD participants. Sudden, substantial increases in inflammation among individuals with relatively low baseline levels of inflammation may have acute effects on muscle function resulting in functional decline. Alternatively, increasing hsCRP levels in the non-PAD group may have identified non-PAD participants with rapidly progressive systemic illness that contributed to functional decline. Rising hsCRP levels may be less significant in a PAD participant, whose hsCRP levels are already relatively high. Collectively, our findings suggest that mechanisms of functional decline may differ between participants with versus without PAD.

To our knowledge, no previous studies have assessed associations between annual changes in hsCRP or D-dimer with functional decline. By promoting muscle proteolysis and impairing tissue repair, inflammation may contribute to impaired quality and quantity of skeletal muscle, which may in turn contribute to functional decline (1–3,9). Inflammation is also an integral component of atherosclerosis (30). Increasing levels of inflammation may signify more extensive or increasing amounts of systemic atherosclerosis that may influence functional performance. Changes in D-dimer levels appear to be less sensitive than those in hsCRP to systemic changes that influence functional performance. This may be because hsCRP is a marker of inflammation, whereas D-dimer is primarily the end-product of fibrinolysis and has a less direct role in promoting systemic inflammation (31,32).

Our study has limitations. First, findings may not be generalizable to participants without annual blood drawing. Second, we cannot rule out the possibility that acute illness resulted simultaneously in increased hsCRP levels and impaired lower extremity functioning. However, participants who reported acute illness prior to a study visit typically rescheduled their appointment. Third, PAD participants in this study had a wide range of PAD severity. Findings may not be generalizable to PAD participants with exclusively mild PAD. Finally, adjusting for baseline performance may introduce bias into analyses of change in functioning over time because of the potential for measurement error in the outcome measure (33).

Previous studies regarding baseline levels of inflammation and subsequent functional decline have shown conflicting results. Among participants in the Women's Health and Aging Study, Ferrucci and colleagues (9) reported significant associations between higher baseline levels of the inflammatory cytokine interleukin-6 and incident disability. However, baseline levels of interleukin-6 and hsCRP were not associated with functional decline among participants in the MacArthur Study of Successful Aging (34). Consistent with this latter study (34), we did not observe significant associations between previous year absolute levels of hsCRP with functional decline in non-PAD participants, after adjusting for annual changes in hsCRP.

The observed drop in hsCRP levels at the first follow-up visit for both PAD and non-PAD participants is of interest and may be due to laboratory drift, as blood analyses for each annual visit were performed in one large batch upon completion of each visit. However, the relative magnitude of change in hsCRP at the first follow-up visit was small and standard deviations for hsCRP measurements were relatively large.

Conclusion

Serial levels of hsCRP may help clinicians assess risk of functional decline. For patients without PAD, substantial increases in hsCRP since the prior year may signify functional decline during the past year. For patients with PAD, higher annual hsCRP levels predict greater functional decline during the subsequent year.

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