D-Dimer, Inflammatory Markers, and Lower Extremity Functioning in Patients With and Without Peripheral Arterial Disease

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Background—We determined whether higher levels of D-dimer, C-reactive protein (CRP), fibrinogen, and serum amyloid A are associated independently with functional impairment in patients with and without peripheral arterial disease (PAD).

Methods and Results—Participants were 370 men and women with PAD (ankle brachial index <0.90) and 231 without PAD. Functional outcomes were 6-minute walk distance and 4-meter walking velocity. A summary performance score combined performance in walking speed, standing balance, and time for 5 repeated chair rises into an ordinal score ranging from 0 to 12 (12=best). Adjusting for age, sex, ankle brachial index, comorbidities, and other potential mediators and confounders, D-dimer levels were associated independently and inversely with performance on all 3 functional measures in the entire cohort and among patients with and without PAD, respectively. Adjusting for known and potential confounders, CRP levels were associated independently with 6-minute walk distance and the summary performance score among participants with PAD. No significant associations were observed between CRP and the functional measures among participants without PAD. Fibrinogen and SAA levels were not associated independently with the functional measures.

Conclusions—Higher D-dimer levels are associated with poorer functioning among individuals with and without PAD. Higher CRP levels were associated with poorer 6-minute walk performance and a lower summary performance score among participants with PAD but not among those without PAD. Additional study is needed to determine whether D-dimer and CRP are involved in the pathophysiology of functional impairment or whether they are simply sensitive markers of the extent of systemic atherosclerosis. (Circulation. 2003;107:3191-3198.)

Key Words: coagulation ■ fibrinolysis ■ epidemiology ■ peripheral vascular disease ■ claudication

Mechanisms of functional impairment in patients with lower extremity peripheral arterial disease (PAD) are not fully understood. Greater lower extremity arterial obstruction, as measured by the ankle brachial index (ABI), is associated with greater functional impairment.1,2 However, to our knowledge, associations between hemostatic or inflammatory markers with lower extremity functioning have not been assessed previously in persons with and without PAD.

Increased levels of D-dimer and inflammatory markers may be associated with functional impairment because they are sensitive measures of the burden of lower extremity and systemic atherosclerosis. D-dimer levels may reflect atherosclerosis severity, because D-dimer is a marker of ongoing fibrin formation and degradation.3-5 Inflammatory markers may also be measures of the extent of atherosclerotic activity.6,7 Alternatively, increased levels of inflammation may weaken muscles, thereby impairing lower extremity functioning.8,9

We determined associations of D-dimer and 3 inflammatory markers (C reactive protein [CRP], fibrinogen, and serum amyloid A [SAA]) with lower extremity functioning in a cohort of men and women with and without PAD. We hypothesized that higher levels of these blood factors would be associated with greater functional impairment.
Methods

Participant Identification
The protocol was approved by the institutional review boards at Northwestern University’s Feinberg School of Medicine and Catholic Health Partners Hospitals. All participants gave written informed consent. PAD participants were identified consecutively from patients diagnosed with PAD in 3 Chicago-area noninvasive vascular laboratories. Half of the participants without PAD were identified from among consecutive patients with normal lower extremity arterial tests in the 3 noninvasive vascular laboratories, and half were identified from among consecutive patients with appointments in a large general internal medicine (GIM) practice at Northwestern. Lists of consecutive patients age 55 and older undergoing lower extremity arterial testing were used to identify potential participants from the noninvasive vascular laboratories. A list of consecutive patients age 55 and older with GIM appointments was used to identify participants systematically from GIM.

Exclusion Criteria
PAD was defined as an ankle brachial index (ABI) < 0.90 among patients with PAD documented in the noninvasive vascular laboratories. A few PAD participants were those with ABI < 0.90 identified from GIM. Absence of PAD was defined as ABI ≥ 0.90 and ≤ 1.50 among patients without PAD identified from the noninvasive vascular laboratories or in GIM.

We excluded individuals originally diagnosed with PAD at the noninvasive vascular laboratory with a normal ABI at their study visit. Individuals originally determined not to have PAD at the noninvasive vascular laboratory who had ABI < 0.90 at the study visit were also excluded. Individuals with ABI > 1.50 were excluded, because this indicates poorly compressible leg arteries and inability to gauge arterial obstruction accurately. The number of participants excluded because of ABI was 151.

Patients with dementia were excluded because of their inability to answer questions accurately. Nursing home residents, wheelchair-bound patients, and patients with foot or leg amputations were excluded because they have severely impaired functioning. Non-English-speaking patients were excluded because investigators were not fluent in non-English languages.

Ankle Brachial Index Measurement
The ABI was measured using established methods. A hand-held Doppler probe (Nicolet Vascular Pocket Dop II) was used to measure systolic pressures in the right brachial artery, right dorsalis pedis, and posterior tibial arteries, left dorsalis pedis and posterior tibial arteries, and left brachial artery. Each pressure was measured twice. The ABI was calculated in each leg by dividing average pressures by the average of the 4 brachial pressures, based on previous study. 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 when the two brachial pressures differed by 10 mm Hg or more in at least one measurement set, because in such cases subclavian stenosis was possible. Lowest leg ABI was used in all analyses.

Blood Collection
A 21-gauge butterfly needle was inserted into an antecubital vein, and the tourniquet was removed immediately. Blood was spun at 3000 rpm for 20 minutes at 4°C in a refrigerated centrifuge. Within 90 minutes of collection, processing and storage in a −70°C freezer were accomplished.

D-Dimer levels
An Asserachrom D-Di kit (Diagnostica Stago) was used to measure fibrin D-dimer. The Asserachrom D-Di kit uses an ELISA procedure to quantitatively determine D-dimer concentration.

High-Sensitivity CRP Levels
CRP levels were determined using a high-sensitivity immunotechnique on the Behring BN II analyzer (Dade Behring). Monoclonal anti-CRP antibodies, coated on polystyrene beads, agglutinate with CRP present in the serum sample. The intensity of the resulting scattered light in the nephelometer was used to determine the CRP content of the sample. This assay is capable of detecting CRP concentration as low as 0.015 mg/dL.

Fibrinogen
Fibrinogen was measured by the method of Clauss using reagents from Hemoliance. The assay was calibrated with standard normal plasma (Universal Coagulation Reference Plasma, Pacific Hemostasis), and the results were calculated using the data management system of the MLA-Electra 800 clot timer.

SAA Levels
SAA levels were measured using an immunotechnique on the Behring BN II analyzer (Dade Behring). Polyclonal anti-SAA antibodies, which are coated on polystyrene beads, agglutinated with SAA present in serum. The intensity of the resulting scatter light in the nephelometer was used to determine the SAA content in the sample.

Comorbidities
Algorithms developed for the Women’s Health and Aging Study and the Cardiovascular Health Study were used to document comorbidities. These algorithms combine data from patient report, physical examination, medical record review, medications, laboratory values, and a primary care physician questionnaire. Comorbidities assessed were those known or suspected to be associated with lower extremity functioning and consisted of the following: angina, diabetes mellitus, myocardial infarction, stroke, heart failure, and pulmonary disease.

Functional Measures
The individuals administering the functional measures had no knowledge of the blood testing results.

Six-Minute Walk
Following a standardized protocol, participants walk up and down a 100-foot hallway for 6 minutes after instructions to cover as much distance as possible.

Four-Meter Walking Velocity
Walking velocity was measured with a 4-meter walk performed at usual pace. Each walk was performed twice. The faster walk in each pair was used in analyses.

Repeted Chair Rises
Participants were asked to sit in a straight-backed chair with arms folded across the chest and stand up 5 times consecutively as quickly as possible without using their arms. Time for 5 chair rises was measured.

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 community dwelling older men and women. A 0 to 4 score is assigned for performance on 4-meter walking velocity, rising from a chair 5 times, and standing balance, respectively, based on cut points derived from normative data of representative community populations. Individuals receive a zero when they are unable to complete the task. The scores of 1 through 4 for each task are assigned based on quartiles of performance for EPESE participants. These scores are summed to obtain the summary performance score, ranging from 0 to 12.
Other Measurements

Height and weight were measured at the study visit. Body mass index (BMI) was calculated as follows: weight (kg)/height² (m). Smoking history was obtained with patient report. All prescription and over-the-counter medications were recorded. We determined which participants were taking a statin cholesterol-lowering medication or aspirin at the time of their study visit.

Statistical Analyses

Differences in clinical characteristics and functional measures between patients with and without PAD were assessed using ANOVA for continuous variables, \( \chi^2 \) tests for categorical variables, and nonparametric Wilcoxon rank sum tests for medians.

Performance in functional measures across quintiles of each blood factor was assessed using general linear models. To assess relations between higher blood factor levels and functional impairment, tests for linear trend were based on linear regression analyses using log-transformed blood factor values. Univariate quintile analyses showed no major nonlinear (i.e., threshold or curvilinear) associations. Thus, linear regression was appropriate.

Using a forward selection method, multiple linear models were used to determine the relative importance of potential mediating factors that explained the association of blood factor levels with each functioning measure. Because blood factor distributions were skewed to the right, natural log-transformed values were used for regression analyses. The functional outcome was the dependent variable for all regression analyses. First, we performed a basic model, in which the relationship between each blood factor and functioning was examined, adjusting for age, sex, and race (African American or non–African American). Second, regression analyses were performed by entering potential mediating factors, including BMI, ABI, diabetes mellitus, cardiac or cerebrovascular disease (myocardial infarction, heart failure, angina, and stroke), pulmonary disease, cigarette smoking (pack-years), statin use (yes/no), and aspirin use (yes/no) separately into the basic model. Based on these results, we selected as the next factor to enter the model the variable that reduced the absolute value of the regression coefficient for log (blood factor) by the largest amount. Once a variable had been selected, it stayed in the model. This selection process continued until no variable considered for addition would further reduce the absolute value of the regression coefficient for log (blood factor). This process was performed for each functional measure and for the logged scale values of D-dimer, CRP, fibrinogen, and SAA.

Stepwise linear regression models were then repeated within the following subgroups: participants with PAD, participants without PAD, PAD participants with exertional leg symptoms, and PAD participants without exertional leg symptoms.

Statistical analyses were performed using SAS statistical software version 8.2 (SAS Institute).

Results

Figure 1 shows reasons for nonparticipation among identified patients. Table 1 shows characteristics of participants with
TABLE 1. Characteristics of Study Participants (n=601)*

<table>
<thead>
<tr>
<th></th>
<th>PAD ABI&lt;0.90</th>
<th>No PAD ABI 0.90 to 1.50</th>
<th>All Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=370)</td>
<td>(n=231)</td>
<td>(n=601)</td>
</tr>
<tr>
<td>Age, y†</td>
<td>71.5 (8.5)</td>
<td>69.2 (8.1)</td>
<td>70.6 (8.4)</td>
</tr>
<tr>
<td>Male, %‡</td>
<td>62.2</td>
<td>53.2</td>
<td>58.7</td>
</tr>
<tr>
<td>African-American race, %</td>
<td>14.0</td>
<td>14.7</td>
<td>14.3</td>
</tr>
<tr>
<td>Ankle brachial index†</td>
<td>0.65 (0.14)</td>
<td>1.09 (0.11)</td>
<td>0.82 (0.25)</td>
</tr>
<tr>
<td>Cigarette smoking, pack-years†</td>
<td>39.1 (35.0)</td>
<td>20.7 (29.0)</td>
<td>32.1 (34.0)</td>
</tr>
<tr>
<td>BMI, kg/m²§</td>
<td>26.4 (5.7)</td>
<td>27.6 (6.2)</td>
<td>26.9 (5.9)</td>
</tr>
<tr>
<td>Diabetes, (%)†</td>
<td>32.7</td>
<td>18.6</td>
<td>27.3</td>
</tr>
<tr>
<td>Cardiac or cerebrovascular disease, %†</td>
<td>60.0</td>
<td>36.8</td>
<td>51.1</td>
</tr>
<tr>
<td>D-dimer, μg/mL (median [IQR])†</td>
<td>0.62 (0.45 to 0.99)</td>
<td>0.46 (0.33 to 0.73)</td>
<td>0.57 (0.39 to 0.88)</td>
</tr>
<tr>
<td>Fibrinogen, mg/dL (median [IQR]§)</td>
<td>364 (320 to 417)</td>
<td>349 (303 to 388)</td>
<td>357 (313 to 405)</td>
</tr>
<tr>
<td>CRP, mg/dL (median [IQR])</td>
<td>0.30 (0.14 to 0.65)</td>
<td>0.27 (0.12 to 0.62)</td>
<td>0.28 (0.13 to 0.65)</td>
</tr>
<tr>
<td>SAA, mg/dL (median [IQR])</td>
<td>0.50 (0.30 to 0.90)</td>
<td>0.40 (0.30 to 0.90)</td>
<td>0.50 (0.30 to 0.90)</td>
</tr>
<tr>
<td>Six-minute walk distance, m†</td>
<td>346 (114)</td>
<td>440 (125)</td>
<td>382 (127)</td>
</tr>
<tr>
<td>Four-meter walking velocity, m/s</td>
<td>0.88 (0.21)</td>
<td>0.96 (0.21)</td>
<td>0.91 (0.21)</td>
</tr>
<tr>
<td>Summary performance score (0–12 score, 12 = best)†</td>
<td>9.5 (2.6)</td>
<td>10.2 (2.3)</td>
<td>9.8 (2.5)</td>
</tr>
</tbody>
</table>

*Values are expressed as mean (SD) unless otherwise indicated. IQR indicates interquartile range.
†P<0.001; ‡P<0.05; §P<0.02 for comparisons between participants with and without PAD.

and without PAD. Among participants with PAD, 73 (20%) had no exertional leg symptoms. Median values of D-dimer and fibrinogen were significantly higher in the PAD group.

We found significant inverse associations between D-dimer and CRP levels with all lower extremity functional measures in unadjusted analyses (Figures 2 and 3). Associations between fibrinogen and SAA and functioning were less linear and not uniformly statistically significant (data not shown).

Table 2 shows results of stepwise regression models, identifying clinical characteristics potentially mediating relationships between D-dimer and each measure of functioning. The significant associations between higher D-dimer levels and poorer functioning are attributable in part to lower ABI values, higher prevalences of cardiac or cerebrovascular disease, a higher prevalence of pulmonary disease, higher BMI, and a higher prevalence of diabetes among participants with greater D-dimer levels (Table 2). Adjusting for confounders, associations between D-dimer and functioning remained statistically significant.

Among participants with PAD, D-dimer was associated independently with 6-minute walk distance (−25.4 m/s per μg/mL, P<0.001), 4-meter walking velocity (−0.035 m/s per μg/mL, P<0.01), and the summary performance score (−0.684 U/μg per mL, P<0.001), adjusting for confounders. In subgroup analyses, regression coefficients relating D-dimer to each functional measure were of greater magnitude among PAD participants who were asymptomatic than among PAD participants with exertional leg symptoms. Regression coefficients for 6-minute walk performance were −32.0 m/mg per dL for asymptomatic PAD participants versus −21.8 m/mg per dL (P<0.02) for PAD participants with exertional leg symptoms, adjusting for confounders. For 4-meter walking velocity, adjusted regression coefficients were −0.066 m/s per mg/dL (P<0.02) and −0.024 m/s per mg/dL, respectively. For the summary performance score, adjusted regression coefficients were −0.93 U/mg per dL (P<0.04) and −0.45 U/mg per dL, respectively (P<0.02).

Among participants without PAD, D-dimer was associated independently with 6-minute walk distance (−41.1 m/μg per mL, P<0.002), 4-meter walking velocity (−0.06 m/s per μg/mL, P<0.01), and the summary performance score (−0.529 U/μg per mL), adjusting for confounders.

In Table 3, factors that potentially mediate the association between CRP and lower extremity performance among participants with and without PAD are presented in decreasing order of magnitude for each functional outcome. Adjusting for known and potential confounders, CRP was associated independently with distance achieved in the 6-minute walk and the summary performance score. Among the subgroup of PAD participants, CRP level was associated independently with 6-minute walk distance (−16.3 m/mg per dL, P<0.003) and the summary performance score (−0.271 U/mg per dL, P<0.02), independently of confounders.

Among PAD participants with no exertional leg symptoms, the magnitude of the regression coefficients relating CRP to functioning was greater than that for participants with exertional leg symptoms (data not shown). Except for the 6-minute walk outcome in PAD patients with no exertional leg symptoms, these relationships were not statistically significant. Among participants without PAD, we found no independent associations between CRP and functioning. We found no significant relations between fibrinogen or SAA and measures of lower extremity functioning, adjusting for confounders (data not shown).

**Discussion**

We found that higher levels of D-dimer were associated with poorer lower extremity functioning among men and women.
with and without PAD, independently of known and potential confounders. These relations persisted when analyses were repeated among subsets of patients with PAD and patients without PAD. The magnitude of the association between D-dimer and leg functioning was greater among asymptomatic PAD participants than among PAD participants with exertional leg symptoms. Our data indicate that D-dimer levels provide additional information related to lower extremity functioning beyond that provided by ABI level, because the relation between higher D-dimer levels and poorer functioning was independent of ABI. Furthermore, D-dimer levels were more consistently associated with functioning than inflammatory markers SAA, fibrinogen, and CRP.

There are several potential explanations for the observed associations between higher D-dimer levels and poorer functioning. First, D-dimer levels may be sensitive measures of the systemic atherosclerotic burden. Greater atherosclerotic burden may be associated with more functional impairment. Second, D-dimer has been shown to induce the synthesis and release of inflammatory cytokines interleukin (IL)-6 and IL-1β. Increased levels of inflammatory cytokines, including IL-6, have been associated with sarcopenia, an age-related reduction in muscle mass and strength. Increased levels of IL-6 are also associated with greater functional decline. Third, D-dimer levels may reflect other unmeasured factors associated with functional impairment.

Figure 2. Unadjusted relationships between D-dimer and lower extremity functioning among men and women with and without PAD (n=601). The number of participants differed by quintile, because some blood factor values at the high or low end of a quintile range were shared by more than one participant. In these instances, the blood values were assigned to the highest corresponding quintile.
Mechanisms proposed for the relation between D-dimer and lower extremity functioning may also apply to the relation between CRP and lower extremity functioning. However, available data suggest that CRP levels may correlate better with risk of acute ischemic events than with severity of atherosclerosis. Alternatively, increased CRP levels reflect an inflammatory state, which in turn may weaken muscles and impair functioning.

In conclusion, D-dimer is inversely and independently related to the degree of functional impairment in a cohort of older men and women with and without PAD. CRP levels are also associated inversely with functional impairment. However, these associations are less robust than for D-dimer. Additional study is needed to determine whether therapies that reduce D-dimer and CRP levels improve lower extremity functioning in men and women with PAD. Additional study is also needed to determine mechanisms of the associations reported here.

Acknowledgments
This study was supported by grants R01-HL58099 and R01-HL64739 from the National Heart Lung and Blood Institute and by grant RR-00048 from the National Center for Research Resources.
TABLE 2. Characteristics Mediating Relationships Between D-Dimer Levels and Functional Outcomes Among Participants With or Without PAD (n=601)*

<table>
<thead>
<tr>
<th>Models</th>
<th>Six-Minute Walk Distance (n=601)</th>
<th>Four-Meter Walking Velocity (n=601)</th>
<th>Summary Performance Score (n=601)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Log D-Dimer Regression Coefficients (m/L per mL)</td>
<td>Log D-Dimer Regression Coefficients (m/s per mL)</td>
<td>Log D-Dimer Regression Coefficients (μL per mL)</td>
</tr>
<tr>
<td>Basic model</td>
<td>0.003†</td>
<td>0.022†</td>
<td>0.012†</td>
</tr>
<tr>
<td>+ ABI</td>
<td>0.019§</td>
<td>0.016§</td>
<td>0.014†</td>
</tr>
<tr>
<td>+ Cardiac or cerebrovascular disease</td>
<td>-0.022‡</td>
<td>+ Pulmonary disease</td>
<td>+ Statin use#</td>
</tr>
<tr>
<td>+ Diabetes‡</td>
<td>+ ABI</td>
<td>+ Pulmonary disease</td>
<td>+ Statin use</td>
</tr>
<tr>
<td>+ Statin use#</td>
<td>+ Cardiac or cerebrovascular disease</td>
<td>+ Cardiac or cerebrovascular disease</td>
<td>+ Cardiac or cerebrovascular disease#</td>
</tr>
</tbody>
</table>

*For each functional outcome, the basic model consisted of log D-dimer, age, sex, and African-American race. Regression coefficients represent the change in each functional outcome for each unit change in log D-dimer level, controlling for other variables in the model. After the basic model, at each step, the variable that explained the greatest difference in performance change per unit change in log D-dimer level (ie, reduced most the absolute value of the regression coefficients for log D-dimer) and still remained statistically significant (at p<0.10) after adjusting for other covariates already in the model was selected to enter. 
†p<0.001; ‡p<0.05; §p<0.01; ¶p<0.04; †p<0.05.
Final stepwise model with all potential mediating factors.

TABLE 3. Characteristics Mediating Relationships Between CRP Levels and Functional Outcomes Among Participants With or Without PAD (n=601)*

<table>
<thead>
<tr>
<th>Models</th>
<th>Six-Minute Walk Distance (n=601)</th>
<th>Four-Meter Walking Velocity (n=601)</th>
<th>Summary Performance Score (n=601)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Log CRP Regression Coefficients, m/L per mg/dL</td>
<td>Log CRP Regression Coefficients, m/s per mg/dL</td>
<td>Log CRP Regression Coefficients, μL per mg/dL</td>
</tr>
<tr>
<td>Basic model</td>
<td>-26.7†</td>
<td>-0.032†</td>
<td>-0.382†</td>
</tr>
<tr>
<td>+ ABI</td>
<td>-21.5†</td>
<td>+ Diabetes‡</td>
<td>+ Pulmonary disease</td>
</tr>
<tr>
<td>+ BMI</td>
<td>-15.9†</td>
<td>+ Pulmonary disease</td>
<td>+ ABI</td>
</tr>
<tr>
<td>+ Diabetes‡</td>
<td>-14.1†</td>
<td>+ Cardiac or cerebrovascular disease</td>
<td>+ Cardiac or cerebrovascular disease#</td>
</tr>
<tr>
<td>+ Statin use‡</td>
<td>-10.5§</td>
<td>+ Statin use§</td>
<td>+ Cardiac or cerebrovascular disease#</td>
</tr>
</tbody>
</table>

*For each functional outcome, the basic model consisted of log CRP, age, sex, and African-American race. Regression coefficients represent the change in each functional outcome for each unit change in log CRP level, controlling for other variables in the model. After the basic model, at each step, the variable that explained the greatest difference in performance change per unit change in log CRP level (ie, reduced most the absolute value of the regression coefficients for log CRP) and still remained statistically significant (at P<0.10) after adjusting for other covariates already in the model was selected to enter.
†p<0.001; ‡p<0.005; §p<0.01; ¶p<0.04; †p<0.05.
Final stepwise model with all potential mediating factors.

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References

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