ORIGINAL RESEARCH

Ankle-Brachial Index and Energy Production in People Without Peripheral Artery Disease: The BLSA

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BACKGROUND: Lower ankle-brachial index (ABI) values within the 0.90 to 1.40 range are associated with poorer mitochondrial oxidative capacity of thigh muscles in cross-sectional analyses. Whether ABI decline is associated with greater declines in thigh muscle oxidative capacity with aging is unknown.

METHOD AND RESULTS: We analyzed data from 228 participants (100 men) of the BLSA (Baltimore Longitudinal Study of Aging), aged 39 to 97 years, with an ABI between 0.9 and 1.40 at baseline and at follow-up (mean follow-up period of 2.8 years). We examined mitochondrial oxidative capacity of the left thigh muscle, by measuring the postexercise phosphocreatine recovery rate constant (kPCr) from phosphorus-31 magnetic resonance spectroscopy. Greater kPCr indicated higher mitochondrial oxidative capacity. Although kPCr was available on the left leg only, ABI was measured in both legs. Longitudinal rates of change (ΔABI) of left and ABI and kPCr of the left thigh muscle were estimated using linear mixed effects models, and their association was analyzed by standardized multiple linear regressions. In multivariate analysis including sex, age, baseline kPCr, both left and right baseline ABI, and ABI change in both legs, (ΔkPCr) was directly associated with ipsilateral (left) ΔABI (standardized [STD]–β = 0.14; P = 0.0168) but not with contralateral (right) ΔABI (P = 0.22). Adjusting for traditional cardiovascular risk factors, this association remained significant (STD–β = 0.18; P = 0.0051). (ΔkPCr) was steeper in White race participants (STD–β = 0.16; P = 0.0122) and body mass index (STD–β = 0.13; P = 0.0479). There was no significant association with current smoking status (P = 0.63), fasting glucose (P = 0.28), heart rate (P = 0.67), mean blood pressure (P = 0.78), and low-density lipoprotein (P = 0.75), high-density lipoprotein (P = 0.82), or triglycerides (P = 0.15).

CONCLUSIONS: In people without peripheral arterial disease, greater decline in ABI over time, but not baseline ABI, was associated with faster decline in thigh mitochondrial oxidative capacity in the ipsilateral leg. Further studies are needed to examine whether early interventions that improve lower extremity muscle perfusion can improve and prevent the decline of muscle energetics.

Key Words: aging ■ epidemiology ■ peripheral vascular disease ■ primary prevention

Impaired walking endurance associated with peripheral artery disease (PAD), defined as an ankle-brachial index (ABI) of <0.90, has been linked to lower mitochondrial oxidative capacity in the muscles of the lower extremities.1 This association may be attributable in part to the discrepancy between oxygen delivery and demand2-3 as well as oxidative damage to myocytes from repeated episodes of ischemia-reperfusion.1,4,5 Even a mildly lower ABI within the range of 0.9 to 1.4 is associated with lower performance in

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mobility tasks\textsuperscript{6–8} and with lower mitochondrial oxidative capacity, assessed by phosphorous-31 magnetic resonance spectroscopy.\textsuperscript{9}

Longitudinal studies have found a decline in ABI with aging in the presence\textsuperscript{10–13} and absence of PAD.\textsuperscript{14} Whether this age-associated longitudinal decline in ABI is also associated with longitudinal reduction in muscle oxidative capacity is unknown.\textsuperscript{9} Hence, we hypothesized that, in participants who are free of PAD, lower ABI at baseline and greater decline in ABI with aging are associated with greater declines in mitochondrial oxidative capacity. If even subclinical decline of ABI is associated with reduced skeletal muscle oxidative capacity, interventions that ameliorate blood flow and muscle perfusion may prevent the decline of mitochondrial function with aging and its consequences.

**METHODS**

**Study Sample**

Participants of the BLSA (Baltimore Longitudinal Study of Aging) are community-dwelling volunteers who undergo 3 consecutive days of medical and physiological testing. Visits occur at intervals of 1 to 4 years and are progressively more frequent with older age.\textsuperscript{15}

A total of 572 repeated measures of postexercise phosphocreatine recovery rate constant ($k_{PCr}$), ABI, and other clinical and laboratory measures were collected from 228 participants between 2013 and 2018. Six participants who reported a diagnosis of PAD and 6 who had ABI <0.90 of either leg were excluded from the analysis.

The Institutional Review Board of the Intramural Research Program of the National Institutes of Health granted ongoing Institutional Review Board approval to the BLSA, and all participants provided written, informed consent. Data and program code associated with this study are available on written request through the corresponding author.

**Phosphorus-31 Magnetic Resonance Spectroscopy**

Thigh muscle mitochondrial oxidative capacity was assessed in the left leg only by magnetic resonance spectroscopy, as previously described.\textsuperscript{16} Briefly, a 3-T magnetic resonance imaging scanner (Achieva; Philips Healthcare, Andover, MA) and a 10-cm phosphorus-31–tuned surface coil (PulseTeq; Surrey, UK) fastened over the left vastus lateralis muscle were used to acquire in vivo spectra of phosphorous-containing metabolites. From a supine position in the bore of the magnet, participants performed a rapid ballistic knee extension exercise, which was first practiced before entering the magnet.\textsuperscript{16,17} Before, during, and after the exercise, pulse-acquired phosphorus-31 spectra were obtained every 6 seconds, yielding a total of 75 spectra acquired over 7.5 minutes, of which the first 5 spectra were recorded at baseline. The pulse sequence incorporated an adiabatic radiofrequency excitation pulse with a 90-degree flip angle, a repetition time of 1.5 seconds, and signal averaging over 4 successive acquisitions for signal/noise ratio enhancement. The length of exercise did not exceed 60 seconds, and the postrecovery period was at least 6 minutes. Exercise was concluded when a reduction in phosphocreatine (PCr) peak height of at least 25% from baseline was observed, with an optimal goal of 66%. If <25% PCr depletion was achieved, then the entire exercise study was repeated, if feasible, after a resting period of ≈10 minutes. Cases with <25% depletion were excluded from the analyses, and all models were statistically adjusted for PCr depletion during exercise to account for its effects on observed associations. Spectra were processed and metabolites were quantified using a publicly available software package (jMRUI) using a nonlinear least-squares algorithm (AMARES).\textsuperscript{18,19}

Phosphocreatine recovery rate was determined by a fit of the postexercise time-dependent PCr peak area to a monoexponential function of the form:

$$PCr(t) = PCr0 + \Delta PCr \times \left[1 - \exp\left(-\frac{t}{\tau PCr}\right)\right]$$

where $PCr0$ is the end-of-exercise PCr peak area (ie, the PCr peak area at $t=0$, the beginning of the recovery period), $\Delta PCr$ is the decrease in peak area from its
Laboratory Studies
At each visit, morning blood samples were taken from the antecubital vein after an 8-hour overnight fast. Plasma triglyceride and total cholesterol concentrations were determined enzymatically by a standard clinical machine (ABA-200ATC Biochromatic Analyzer; Abbott Laboratories, Irving, TX). High-density lipoprotein cholesterol concentrations were determined via an established precipitation procedure. Low-density lipoprotein (LDL) cholesterol concentrations were estimated using the Friedewald formula. Glucose concentration was measured via the glucose oxidase method using a standard instrument (Beckman Instruments, Inc, Fullerton, CA). CRP (C-reactive protein) was measured via ELISA (Immundiagnostik AG, Bensheim, Germany). Erythrocyte sedimentation rate (ESR) was measured in a Sediplast tube (LP Italiano, Venice, Italy).

Statistical Analysis
Given the observed differences in ABI by sex, descriptive characteristics of the sample at baseline were reported and compared between men and women. For categorical variables, proportions were compared using χ² statistics, whereas continuous variables were reported as mean±SD, and comparisons were made via Student t test. Given the relatively small sample size and the absence of significant sex differences in kPCr, subsequent analyses were not stratified by sex but included sex as a covariate and sex interaction terms to test for sex differences in associations.

Rates of change in left and right ABI and left thigh muscle kPCr were estimated by linear mixed effects models, which allow for unbalanced, unequally spaced observations, such as those of the BLSA. The general approach for using this method was described previously in detail. In summary, individual longitudinal rates of change \( \text{Rate of change} \) were calculated by fitting separate linear mixed effects models for each variable, regressing the indexed variable against follow-up time in years as a random effect (ie, the estimated individual variation from the population average slope was used to calculate the individual rate of change \( [\text{Rate of change}] \)).

Multiple linear regression models were then used to examine the independent association between left and right ABI, and left and right kPCr. The initial model fitted for kPCr as a function of independent variables, including sex, baseline age, baseline kPCr, PCr depletion, and left ABI, in addition to rates of change of PCr depletion and left ABI. The second model included right ABI and its rate of change (but not left ABI and its rate of change), whereas the third model adjusted for covariates and traditional cardiovascular risk factors, including pulse wave velocity, race, current smoking, fasting glucose, body mass index, mean
arterial pressure, and blood lipids. In additional models, left leg composition and inflammatory markers and their changes over time, baseline medications, and LDL_{change} were explored as potential correlates of (kPCr)_{change}. Sex-(ABI)_{change} interaction terms were included to assess sex differences.

To illustrate the association between ABI and kPCR, baseline left ABI range was divided into 2 groups (namely, borderline/low-normal [0.90–1.10] and high-normal [1.11–1.4]). Similarly, left (ABI)_{change} was categorized into 3 groups based on tertiles. Least-squares adjusted means of (kPCr)_{change} (including variables in Table 2, model 1) were calculated for left baseline ABI and (ABI)_{change} groups and compared using ANCOVA followed by a post hoc Tukey test. For all analyses, \( P < 0.05 \) was the threshold for significance, and all analyses were performed via SAS for Windows (Version 9.4; Cary, NC).

RESULTS

The average baseline age of the study population was 75 years (range, 39–97 years). On average, participants had 3 visits and a mean follow-up of 2.8 years (SD, 1.2 years) (Table 1). Of participants, 70% were White race and 2.2% were current smokers. There were no differences between men and women in mean arterial pressure, triglyceride levels, left thigh muscle oxidative capacity (kPCR), phosphocreatine depletion, and CRP. However, compared with women, men had greater fasting glucose, body mass index, ABI, pulse wave velocity, and left leg lean/fat ratio but lower heart rate, LDL and high-density lipoprotein levels, and ESR.

The mean and SD of (kPCr)_{change} was 0.0000568±0.0000556 ms\(^{-1}\)/y, while that of left (ABI)_{change} was 0.00163±0.0082/y relative to a mean intravisit left ABI SD of 0.0395. Figure 1 illustrates the bivariate association between kPCR and left ABI rates of change. In multivariate linear regression analysis, left (ABI)_{change}, but not baseline left ABI, was a significant independent predictor of (kPCr)_{change} (standardized \( \beta = 0.1440 \) \( [P = 0.0168] \) and standardized \( \beta = 0.0400 \) \( [P = 0.52] \), respectively; Table 2, model 1). (kPCr)_{change} was not significantly associated with baseline right ABI or right (ABI)_{change} \( (P = 0.81 \) and \( P = 0.22 \), respectively; Table S1, model 1). The association of left (ABI)_{change} with (kPCr)_{change} was independent of baseline right ABI and right (ABI)_{change} before (Table S1, model 2) and after adjusting for traditional cardiovascular risk factors (Table S1, model 3). The association of left (ABI)_{change} with (kPCr)_{change} was also independent of initial age, baseline kPCR, and (PCr depletion)_{change} (Table 2, model 1), and remained significant after adjusting for additional covariates, including traditional cardiovascular risk factors (Table 2, model 2). White

Table 1. Baseline Characteristics of the Study Population

| Variable              | Total (n=228) | Men (n=100) | Women (n=128) | \( P \) value |
|-----------------------|--------------|-------------|---------------|--------------|
| Initial age, y        | 75.0±9.5     | 75.8±8.9    | 74.3±10.0     | 0.2450       |
| Follow-up time, y     | 2.8±1.2      | 2.8±1.2     | 2.7±1.2       | 0.5642       |
| No. of follow-ups     | 2.5±0.8      | 2.6±0.9     | 2.5±0.8       | 0.5168       |
| Race (White)          | 160 (70.2)   | 78 (78.0)   | 82 (64.1)     | 0.0284       |
| Current smoker        | 5 (2.2)      | 4 (4.0)     | 1 (0.8)       | 0.1713       |
| Fasting glucose, mg/dL| 95.6±11.9    | 98.3±14.0   | 93.4±9.5      | 0.0048       |
| BMI, kg/m\(^2\)       | 26.6±4.2     | 27.6±3.9    | 25.9±4.3      | 0.0016       |
| HR, bpm               | 70.7±11.5    | 68.4±11.2   | 72.4±11.4     | 0.0094       |
| RB MAP, mm Hg         | 89.8±11.2    | 90.5±8.9    | 89.2±12.6     | 0.3680       |
| LDL, mg/dL            | 95.9±30.7    | 88.5±27.7   | 101.7±31.8    | 0.0012       |
| HDL, mg/dL            | 65.3±18.4    | 55.9±15.1   | 72.6±17.4     | <0.0001      |
| Triglycerides, mg/dL  | 92.2±49.9    | 100.0±62.3  | 86.2±36.8     | 0.0517       |
| PWV, m/s              | 7.8±2.1      | 8.4±2.3     | 7.4±1.8       | 0.0005       |
| kPCR, ms\(^{-1}\)     | 0.0200±0.0047 | 0.0205±0.0048 | 0.0195±0.0045 | 0.1199       |
| PCr depletion, %      | 39.7±9.2     | 39.8±9.4    | 39.7±9.0      | 0.9521       |
| Left ABI              | 1.17±0.08    | 1.20±0.08   | 1.16±0.08     | 0.0003       |
| Right ABI             | 1.17±0.08    | 1.19±0.08   | 1.16±0.08     | 0.0012       |
| Left leg lean/fat ratio| 1.89±0.95   | 2.88±0.87   | 1.27±0.40     | <0.0001      |
| CRP, mg/L             | 2.06±2.99    | 2.09±3.06   | 2.03±2.94     | 0.8869       |
| ESR, mm/h             | 12.2±11.6    | 9.2±10.2    | 14.5±12.1     | 0.0005       |

Data are given as mean±SD or number (percentage). ABI indicates ankle-brachial index; BMI, body mass index; bpm, beats per minute; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HDL, high-density lipoprotein; HR, heart rate; kPCR, postexercise phosphocreatine recovery rate constant; LDL, low-density lipoprotein; PCr, phosphocreatine; PWV, pulse wave velocity; and RB MAP, right brachial mean arterial pressure.
race and higher body mass index were associated with greater increase in (kPCr)Change (standardized $\beta=0.1560$ [$P=0.0122$] and standardized $\beta=0.1293$ [$P=0.0479$], respectively). Baseline pulse wave velocity, current smoking, fasting glucose, heart rate, mean arterial pressure, and cholesterol levels were not significantly associated with (kPCr)Change. Also, left thigh muscle lean/fat composition ratio and CRP and their changes, baseline medications, and LDL Change were not associated with (kPCr)Change (Tables S2 through S5). ESRChange was directly associated with (kPCr)Change, but only after adjusting for covariates and cardiovascular risk factors ($P=0.0495$; Table S4, model 4). Left (ABI) Change remained an independent and significant predictor of (kPCr)Change after adjustment for all these potential founders. Via multiple regression analysis, the longitudinal left ABI-kPCr relationship had a power of 0.62. To illustrate the association between left ABI and kPCr, we plotted model-adjusted means of (kPCr)Change (based on Table 2, model 1) for baseline left ABI categories (0.90–1.10 and 1.11–1.4) and left (ABI)Change tertiles. As shown in Table 2, there was no significant difference between the 2 baseline ABI groups (Figure 2A). However, those in the highest tertile of left (ABI)Change had significantly higher mean (kPCr)Change than those in the lowest tertile (Figure 2B).

**DISCUSSION**

**Principal Findings**

In this study, we found that among people without PAD, ABI longitudinal decline, but not baseline value, was associated with a decline in thigh muscle oxidative capacity of the same leg but not of the contralateral leg; this longitudinal association remained significant after adjusting for covariates and cardiovascular risk factors.

**Linear Association Between ABI and Muscle Oxidative Capacity**

This study is consistent with our previously published findings that, when compared with those with high-normal ABI (1.10–1.40), individuals with modestly reduced ABI (0.90–1.09) are more likely to have lower thigh muscle mitochondrial oxidative capacity, as assessed by kPCr, in cross-sectional analyses. These new results, however, add a longitudinal dimension that reinforces the idea that even subclinical reduction of ABI negatively impacts skeletal muscle oxidative capacity. The association appears linear, suggesting that declines in ABI affect oxidative capacity at any level within the normal ABI range studied herein, independent of initial ABI. However, further studies with a larger sample size may be needed to finally determine whether impairment of oxidative capacity only critically occurs below a certain ABI threshold.

The underlying mechanism of this association remains undefined, but these findings might indicate that low-normal ABI is indicative of limited ability to increase blood flow during exercise, leading to reduced postexercise oxidative capacity. The significant association of (kPCr)Change with changes in ipsilateral but not contralateral ABI suggests that local flow-limiting factors, such as structural plaques or impaired endothelial reactivity,
may contribute to this phenomenon by limiting oxygen delivery to mitochondria. Such theories are also consistent with our prior work indicating that differences in muscle perfusion partly explain the age-associated decline in muscle oxidative capacity.34 Interestingly, we found that the association of hemodynamics and muscle energetic changes was not accounted for by typical age-associated changes, including changes in muscle/fat ratio. Further studies examining systemic and local contributors to this process, including changes in type I versus type II muscle fibers, femoral artery blood flow, and endothelial function with aging, are needed.

### Indications of an Early Relationship Between ABI and Muscle Energetics

One of the interesting findings of this analysis is that the heterogeneity in ABI changes was concordant with that in muscle oxidative capacity; specifically, our analysis of the consistency between change in ABI and change in kPCR showed that participants in the lowest tertile (negative changes) and those in the highest tertile (positive changes) of ABI rate of change were more likely to have concordant changes in kPCR (Figure 2B).

Although we cannot make any causal statements based on an observational study, the changes observed in this analysis (ie, increasing and decreasing ABI with corresponding changes in kPCR) suggest a possible dynamic relationship between these 2 parameters. Such a dynamic relationship, if it exists, would not be explained only by flow-limiting lesions, which tend to be fixed or progressive. However, more labile hemodynamic alterations that ensue with arterial aging, such as changes in pressure wave reflection and peripheral pulse pressure amplification, can contribute to the changes in ABI observed in this healthy cohort.

It is possible that the reduction in oxidative capacity observed in this study might be reversible. Furthermore, even fluctuations in perfusion may cause a vicious cycle of ischemia-reperfusion injury that causes irreversible damage and in some individuals may evolve into clinically overt PAD (ie, ABI <0.90).1,4,5 However, these hypotheses could not be tested because of limitations in the number of follow-up visits with complete data in this study. Hence, our findings call for further investigations, including clinical trials testing the hypothesis that increasing lower extremity perfusion in individuals with borderline/low-normal ABI values may help preserve mitochondrial function and possibly prevent subclinical decline with aging.

### Limitations

First, the association between change in ABI and change in oxidative capacity remained significant after adjusting for multiple potential confounders but was

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**Table 2. Multiple Linear Regression Models Predicting (kPCr)\textsubscript{change} and Considering Left ABI and Left (ABI)\textsubscript{change} (Model 1) and Covariates and Cardiovascular Risk Factors (Model 2)**

| Variable                                      | Model 1 | Model 2 |
|-----------------------------------------------|---------|---------|
| Intercept                                     | 1.80E-03 | 2.08E-03 |
| Initial age, y                                | −8.05E-06 | −1.09E-05 |
| Sex (men)                                     | −5.44E-05 | 3.86E-05  |
| kPCR, ms\(^{-1}\)                              | −6.64E-02 | −6.94E-02 |
| PCr depletion, %                              | −1.65E-06 | −4.19E-06 |
| (PCr depletion)\textsubscript{change}, %/y   | −1.13E-04 | −1.26E-04 |
| Left ABI                                      | 2.77E-04  | 2.26E-04  |
| Left (ABI)\textsubscript{change}, y\(^{-1}\) | 9.81E-02  | 1.19E-02  |
| [PWV]\textsubscript{change}, m/s per y        | ...      | ...      |
| Race (White)                                  | ...      | ...      |
| Current smoker                                | ...      | ...      |
| Fasting glucose, mg/dL                        | ...      | ...      |
| BMI, kg/m\(^2\)                               | ...      | ...      |
| HR, bpm                                       | ...      | ...      |
| RB MAP, mm Hg                                 | ...      | ...      |
| LDL, mg/dL                                    | ...      | ...      |
| HDL, mg/dL                                    | ...      | ...      |
| Triglycerides, mg/dL                          | ...      | ...      |

ABI indicates ankle-brachial index; BMI, body mass index; bpm, beats per minute; Change, longitudinal rates of change; HDL, high-density lipoprotein; HR, heart rate; kPCR, postexercise phosphocreatine recovery rate constant; LDL, low-density lipoprotein; PCr, phosphocreatine; PWV, pulse wave velocity; RB MAP, right brachial mean arterial pressure; and ST\(\beta\), standardized \(\beta\) coefficient.
modest in magnitude. Thus, these findings should be interpreted with caution and should be replicated in an independent population and with longer follow-up. Second, the BLSA is a study of healthy aging with well-educated participants who have relatively high socioeconomic status. Thus, these findings may not extrapolate to the general population. Third, the BLSA is an observational study, and therefore, the associations observed herein are not sufficient to conclude causal relationships between hemodynamics and oxidative metabolism. Fourth, this study did not measure plaque burden, either proximally or distally, preventing the examination of its contribution to the associations observed. Fifth, a relationship between mitochondrial activity and functional performance is yet to be established. Sixth, the relatively small sample size and short longitudinal follow-up time of our study might have produced unstable longitudinal estimates that prevented observations of nonlinear associations and sex differences that should be examined in future studies. Seventh, this study lacks advanced hemodynamic characterizations, including the evaluation of femoral endothelial function, and further studies are needed to examine the role of hemodynamic properties in the longitudinal changes observed in muscle energetics.

**CONCLUSIONS**

Modest longitudinal decline in ABI in people without PAD was associated with a simultaneous decline in thigh muscle oxidative capacity. A dynamic relationship

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**Figure 2.** Postexercise phosphocreatine recovery rate constant ($k_{\text{PCr}}$) mean rates of change for those with baseline left ankle-brachial index (ABI) in the borderline/low-normal (left) and normal (right) ranges (A) and $k_{\text{PCr}}$ mean rates of change for lower, middle, and upper tertile groups of left ABI rate of change (B). Least-squares (LS).

*P*<0.05 vs lower.
between ABI and muscle energy is suggested by the predominantly concordant changes in ABI and muscle oxidative capacity and the lack of association between kPCr rate of change and baseline ABI. Future studies are necessary to determine whether interventions that increase lower extremity perfusion prevent the decline in lower extremity oxidative capacity and mobility impairment observed in many aging individuals.

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Supplemental Material
Tables S1–S5

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SUPPLEMENTAL MATERIAL
Table S1. Model predicting \((k\text{PCr})_{\text{Change}}\) from right ABI and its change (Model 1), and \((k\text{PCr})_{\text{Change}}\) predicted by left ABI change in models that adjust for right ABI and its change before (Model 2) and after (Model 3) adjustment for covariates and cardiovascular risk factors.

| Variable (Units) | Model 1 | | Model 2 | | Model 3 | |
|-----------------|---------|------------------|---------|----------|---------|------------------|---------|----------|---------|------------------|---------|----------|---------|
| Intercept       | 2.31E-03| 0.0000           | 0.0002  | 2.00E-03| 0.0000  | 0.0019           | 2.37E-03| 0.0000  | 0.0077  |                   |         |          |         |
| Initial Age (Years) | -8.85E-06| -0.1524          | 0.0072  | -8.32E-06| -0.1434 | 0.0113           | 1.16E-05| -0.1988 | 0.0021  |                   |         |          |         |
| Sex (Men)       | -4.32E-05| -0.0385          | 0.4951  | -4.73E-05| -0.0421 | 0.4539           | 1.99E-05| -0.0177 | 0.7965  |                   |         |          |         |
| \(k\text{PCr} \text{ (ms}^{-1}\)) | -6.63E-02| -0.5563          | <0.0001 | -6.70E-02| -0.5620 | <0.0001          | -7.03E-02| -0.5960 | <0.0001 |                   |         |          |         |
| PCr Depletion (%) | -1.67E-06| -0.0277          | 0.7212  | -1.43E-06| -0.0238 | 0.7574           | 3.57E-06| -0.0607 | 0.4725  |                   |         |          |         |
| \((\text{PCr Depletion})_{\text{Change}} \text{ (\%} \text{Year}^{-1}\)) | -1.12E-04| -0.2098          | 0.0079  | -1.14E-04| -0.2135 | 0.0066           | -1.25E-04| -0.2379 | 0.0050  |                   |         |          |         |
| Left ABI        | -       | -                | -       | 9.01E-04| 0.1294  | 0.2121           | 1.31E-03| 0.1872  | 0.0803  |                   |         |          |         |
| Left ABI_{\text{Change}} \text{ (Year}^{-1}\) | -       | -                | -       | 1.16E-02| 0.1698  | 0.0277           | 1.67E-02| 0.2455  | 0.0022  |                   |         |          |         |
| Right ABI       | -1.02E-04| -0.0146          | 0.8124  | -7.72E-04| -0.1098 | 0.2772           | -1.33E-03| -0.1872 | 0.0693  |                   |         |          |         |
| Right ABI_{\text{Change}} \text{ (Year}^{-1}\) | 4.08E-03| 0.0739           | 0.2178  | -1.66E-03| -0.0301 | 0.6910           | -5.31E-03| -0.0949 | 0.2235  |                   |         |          |         |
| PWV_{\text{Change}} \text{ (m} \text{s}^{-1} \text{Year}^{-1}\) | -       | -                | -       | -       | -       | -               | -       | -       | -       |                   |         |          |         |
| Race (White)    | -       | -                | -       | -       | -       | -               | -       | -       | -       |                   |         |          |         |
| Current Smoker  | -       | -                | -       | -       | -       | -               | -       | -       | -       |                   |         |          |         |
| Fasting Glucose (mg/dL) | -       | -                | -       | -       | -       | -               | -       | -       | -       |                   |         |          |         |
| BMI (kg/m\(^2\)) | -       | -                | -       | -       | -       | -               | -       | -       | -       |                   |         |          |         |
| HR (bpm)        | -       | -                | -       | -       | -       | -               | -       | -       | -       |                   |         |          |         |
| RB MAP (mmHg)   | -       | -                | -       | -       | -       | -               | -       | -       | -       |                   |         |          |         |
| LDL (mg/dL)     | -       | -                | -       | -       | -       | -               | -       | -       | -       |                   |         |          |         |
| HDL (mg/dL)     | -       | -                | -       | -       | -       | -               | -       | -       | -       |                   |         |          |         |
| Triglycerides (mg/dL) | -       | -                | -       | -       | -       | -               | -       | -       | -       |                   |         |          |         |

ABI (ankle-brachial index), PWV (pulse wave velocity), BMI (body mass index), HR (heart rate), RB MAP (right brachial mean arterial pressure), LDL (low-density lipoprotein), HDL (high-density lipoprotein), STβ (standardized β coefficient)
Table S2. Models predicting \((k_{\text{PCr}})_{\text{change}}\) that consider longitudinal change in LDL before (Model 1) and after (Model 2) adjustment for covariates and cardiovascular risk factors.

| Variable (Units)          | Model 1   |       |       | Model 2   |       |       |
|---------------------------|-----------|-------|-------|-----------|-------|-------|
|                           | \(\beta\) | \(P\) |       | \(\beta\) | \(P\) |       |
| Intercept                 | 1.71E-03  | 0.0055|       | 2.02E-03  | 0.0203|       |
| Initial Age (Years)       | -7.69E-06| 0.0183|       | -1.07E-05| 0.0043|       |
| Sex (Men)                 | -5.47E-05| 0.3779|       | -4.02E-05| 0.5984|       |
| \(k_{\text{PCr}}\) (ms\(^{-1}\)) | -6.66E-02| <0.0001|       | -7.04E-02| <0.0001|       |
| PCr Depletion (%)         | -1.61E-06| 0.7259|       | -4.03E-06| 0.4161|       |
| (PCr Depletion)\(_{\text{change}}\) (%/Year) | -1.12E-04| 0.0065|       | -1.25E-04| 0.0044|       |
| Left ABI                  | 3.31E-04  | 0.447 |       | 2.90E-04  | 0.5277|       |
| Left ABI\(_{\text{change}}\) (Year\(^{-1}\)) | 9.88E-03| 0.0158|       | 1.18E-02  | 0.0056|       |
| PWV\(_{\text{change}}\) (m/s/Year) | - | - | 2.07E-04 | 0.0903|       |
| Race (White)              | -         | -     |       | 1.90E-04  | 0.0136|       |
| Current Smoker            | -         | -     |       | -7.91E-05| 0.7302|       |
| Fasting Glucose (mg/dL)   | -         | -     |       | -3.29E-06| 0.2754|       |
| BMI (kg/m\(^2\))         | -         | -     |       | 1.71E-05  | 0.0547|       |
| HR (bpm)                  | -         | -     |       | -1.37E-06| 0.6390|       |
| RB MAP (mmHg)             | -         | -     |       | 5.78E-07  | 0.8483|       |
| LDL (mg/dL)               | -         | -     |       | 8.99E-08  | 0.9368|       |
| HDL (mg/dL)               | -         | -     |       | 2.24E-07  | 0.9176|       |
| Triglycerides (mg/dL)     | -         | -     |       | -1.02E-06| 0.1697|       |
| LDL\(_{\text{change}}\) (mg/dL/Year) | 7.45E-06| 0.1528|       | 7.35E-06  | 0.2380|       |

ABI (ankle-brachial index), PWV (pulse wave velocity), BMI (body mass index), HR (heart rate), RB MAP (right brachial mean arterial pressure), LDL (low-density lipoprotein), HDL (high-density lipoprotein)
Table S3. Models predicting $(\Delta^{kPCr})$ that consider left thigh composition and its longitudinal change before (Model 1) and after (Model 2) adjustment for covariates and cardiovascular risk factors.

| Variable (Units) | Model 1 | Model 2 |
|------------------|---------|---------|
|                  | $\beta$ | $P$     | $\beta$ | $P$     |
| Intercept        | 1.91E-03| 0.0020  | 2.77E-03| 0.0023  |
| Initial Age (Years) | -7.83E-06| 0.0171 | -1.16E-05| 0.0020 |
| Sex (Men)        | -6.41E-06| 0.9426 | 8.13E-05| 0.5111  |
| $k$ PCr (ms$^{-1}$) | -6.49E-02| <0.0001| -6.93E-02| <0.0001|
| PCr Depletion (%) | -1.75E-06| 0.7060 | -3.94E-06| 0.4280  |
| (PCr Depletion)$_{\text{Change}}$ (%/Year) | -1.09E-04| 0.0086 | -8.12E-04| 0.0090  |
| Left ABI         | 1.87E-04| 0.6684 | 8.12E-05| 0.8599  |
| Left ABI$_{\text{Change}}$ (Year$^{-1}$) | 1.02E-02| 0.0130 | 1.25E-02| 0.0034  |
| PWV$_{\text{Change}}$ (m/s/Year) | - - | 1.95E-04| 0.1190  |
| Race (White)     | - - | 1.83E-04| 0.0189  |
| Current Smoker   | - - | -1.61E-04| 0.4809  |
| Fasting Glucose (mg/dL) | - - | -4.25E-06| 0.1616  |
| BMI (kg/m$^2$)   | - - | 1.01E-05| 0.3267  |
| HR (bpm)         | - - | -2.67E-06| 0.3677  |
| RB MAP (mmHg)    | - - | 6.54E-07| 0.8293  |
| LDL (mg/dL)      | - - | -1.84E-07| 0.8656  |
| HDL (mg/dL)      | - - | 3.08E-07| 0.8862  |
| Triglycerides (mg/dL) | - - | 1.01E-06| 0.1758  |
| Left Leg Lean to Fat Ratio | -3.24E-05| 0.4937 | -6.21E-05| 0.3006  |
| (Left Leg Lean to Fat Ratio)$_{\text{Change}}$ (Year$^{-1}$) | 9.98E-05| 0.8590 | 4.56E-04| 0.4253  |

ABI (ankle-brachial index), PWV (pulse wave velocity), BMI (body mass index), HR (heart rate), RB MAP (right brachial mean arterial pressure), LDL (low-density lipoprotein), HDL (high-density lipoprotein)
Table S4. Models predicting \((k\text{PCr})_{\text{Change}}\) that consider inflammatory markers (CRP and ESR) and their longitudinal changes before (Models 1 and 3) and after (Models 2 and 4) adjustment for covariates and cardiovascular risk factors.

| Variable (Units)                  | Model 1       | Model 2       | Model 3       | Model 4       |
|-----------------------------------|---------------|---------------|---------------|---------------|
|                                  | \(\beta\)    | \(P\)         | \(\beta\)    | \(P\)         | \(\beta\)    | \(P\)         | \(\beta\)    | \(P\)         | \(\beta\)    | \(P\)         |
| Intercept                        | 2.05E-03      | 0.0019        | 2.27E-03      | 0.0119        | 1.93E-03      | 0.0023        | 2.07E-03      | 0.0175        |
| Initial Age (Years)              | -8.96E-06     | 0.0104        | -1.05E-05     | 0.0063        | -7.00E-06     | 0.0354        | -1.12E-05     | 0.0046        |
| Sex (Men)                        | -6.16E-05     | 0.3509        | -5.41E-05     | 0.4867        | -7.12E-05     | 0.2659        | -1.93E-05     | 0.8043        |
| \(k\text{PCr} \text{m}^{-1}\)   | -6.67E-02     | <0.0001       | -7.05E-02     | <0.0001       | -6.81E-02     | <0.0001       | -7.15E-02     | <0.0001       |
| PCr Depletion (%)                | -3.89E-06     | 0.4289        | -4.92E-06     | 0.3307        | -2.28E-06     | 0.6246        | -4.35E-06     | 0.3867        |
| (PCr Depletion)\(_{\text{Change}}\) (%/Year) | -1.24E-04     | 0.0048        | -1.27E-04     | 0.0043        | -1.15E-04     | 0.0077        | -1.15E-04     | 0.0132        |
| Left ABI                         | 2.30E-04      | 0.6179        | 1.21E-04      | 0.7950        | 1.94E-04      | 0.6649        | 2.85E-04      | 0.5431        |
| Left \(\text{ABI}_{\text{Change}}\) (Year\(^{-1}\)) | 1.18E-02      | 0.0076        | 1.25E-02      | 0.0051        | 9.74E-02      | 0.0217        | 1.25E-02      | 0.0484        |
| PWV\(_{\text{Change}}\) (m/s/Year) | - -           | 2.05E-04      | 0.1071        | - -           | 2.06E-04      | 0.0939        | - -           | - -           |
| Race (White)                     | - -           | 1.95E-04      | 0.0147        | - -           | 2.11E-04      | 0.0104        | - -           | - -           |
| Current Smoker                   | - -           | 5.60E-05      | 0.8304        | - -           | -1.43E-04     | 0.5356        | - -           | - -           |
| Fasting Glucose (mg/dL)          | - -           | -3.38E-06     | 0.2675        | - -           | -3.85E-06     | 0.2058        | - -           | - -           |
| BMI (kg/m\(^2\))                | - -           | 1.50E-05      | 0.1047        | - -           | 1.82E-05      | 0.0451        | - -           | - -           |
| HR (bpm)                         | - -           | -1.29E-06     | 0.6643        | - -           | -9.90E-07     | 0.7399        | - -           | - -           |
| RB MAP (mmHg)                    | - -           | 1.11E-06      | 0.7186        | - -           | 3.22E-07      | 0.9157        | - -           | - -           |
| LDL (mg/dL)                      | - -           | -5.89E-07     | 0.5931        | - -           | -3.69E-07     | 0.7329        | - -           | - -           |
| HDL (mg/dL)                      | - -           | 7.99E-07      | 0.7141        | - -           | 7.79E-07      | 0.7189        | - -           | - -           |
| Triglycerides (mg/dL)            | - -           | -8.48E-07     | 0.2607        | - -           | -1.00E-06     | 0.1828        | - -           | - -           |
| CRP (mg/L)                       | -6.95E-06     | 0.5559        | -2.80E-07     | 0.9817        | - -           | - -           | - -           | - -           |
| CRP\(_{\text{Change}}\) (mg/L/Year) | -1.12E-04     | 0.0927        | -7.46E-05     | 0.2720        | - -           | - -           | - -           | - -           |
| ESR (mm/Hour)                    | - -           | - -           | - -           | - -           | -1.21E-06     | 0.6716        | 4.51E-06      | 0.1832        |
| ESR\(_{\text{Change}}\) (mm/Hour/Year) | - -           | - -           | - -           | - -           | -3.80E-05     | 0.0935        | 4.83E-05      | 0.0495        |

ABI (ankle-brachial index), PWV (pulse wave velocity), BMI (body mass index), HR (heart rate), RB MAP (right brachial mean arterial pressure), LDL (low-density lipoprotein), HDL (high-density lipoprotein), CRP (C-reactive protein), ESR (erythrocyte sedimentation rate)
Table S5. Models predicting \((kPCr)_{\text{change}}\) that consider medications at baseline after adjustment for covariates and cardiovascular risk factors.

| Variable (Units) | Vasodilators | Other Cardiac Meds | Antihypertensives | Diuretics | Peripheral Vasodilators | Beta Blockers | Calcium Antagonists | RAAS Inhibitors | Lipid Drugs | Diabetes Drugs |
|-----------------|--------------|-------------------|-------------------|-----------|-------------------------|--------------|---------------------|-----------------|-------------|---------------|
| Intercept       | β            | P                 | β                 | P         | β                       | P            | β                   | P               | β           | P             |
| Initial Age (Years) | -1.09E-05 | 0.0035            | -1.13E-05          | 0.0026     | -1.09E-05               | 0.0037       | -1.10E-05          | 0.0040          | -1.18E-05   | 0.0019        |
| Sex (Men)       | -3.78E-05 | 0.6210            | -3.47E-05          | 0.6488     | -4.03E-05               | 0.6060       | -3.90E-05          | 0.6694          | -6.594E-05  | 2.94E-05      |
| %PCr depletion (% | 2.90E-03    | 0.0165             | 2.09E-03           | 0.0180     | 2.09E-03                | 0.0165       | 1.90E-03           | 0.0299          | 2.15E-03    | 0.0150        |
| ABI (ankle-brachial index) | 2.04E-04    | 0.4147             | 2.04E-04           | 0.6190     | 1.74E-05                | 0.0040       | 1.18E-05           | 0.0040          | 1.18E-05    | 0.0040        |
| PWV (pulse wave velocity) | 2.05E-04    | 0.6820             | 2.09E-03           | 0.3948     | 4.21E-06                | 0.4000       | 4.19E-06           | 0.3990          | 4.24E-06    | 0.4011        |
| BMI (kg/m²)     | 2.03E-04    | 0.0053             | 2.03E-04           | 0.0032     | 2.03E-04                | 0.0043       | 2.03E-04           | 0.0043          | 2.03E-04    | 0.0043        |
| Race (White)    | 1.94E-04    | 0.0120             | 1.95E-04           | 0.0117     | 1.94E-04                | 0.0122       | 1.91E-04           | 0.0135          | 1.90E-04    | 0.0138        |
| Current Smoker  | -1.10E-04   | 0.6294             | -1.24E-04          | 0.5868     | -1.12E-04               | 0.6243       | -9.72E-05          | 0.6696          | -9.14E-04   | 0.6190        |
| Fasting Glucose (mg/dL) | -3.31E-06 | 0.2754             | -2.94E-06          | 0.3381     | -3.23E-06               | 0.2877       | -3.55E-06          | 0.2441          | -2.73E-06   | 0.3717        |
| HDL (mg/dL)     | 4.85E-07    | 0.8221             | 4.96E-07           | 0.8170     | 5.09E-07                | 0.8263       | 6.04E-07           | 0.8297          | 7.82E-07    | 0.7179        |
| Triglycerides (mg/dL) | -1.04E-06 | 0.6150             | -1.00E+06          | 0.1790     | 1.06E-06                | 0.1546       | -1.02E-06          | 0.1715          | -1.16E-06   | 0.1370        |
| Medication      | 1.52E-04    | 0.6420             | 1.69E-04           | 0.1477     | 3.53E-05                | 0.8406       | 1.41E-04           | 0.3766          | 2.36E-04    | 0.2611        |