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Plasma Acylcarnitines Are Associated With Physical Performance in Elderly Men

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Background. Metabolic profiling might provide insight into the biologic underpinnings of disability in older adults.

Methods. A targeted mass spectrometry–based platform was used to identify and quantify 45 plasma acylcarnitines in 77 older men with a mean age of 79 years and average body mass index of 28.4 kg/m^2. To control for type I error inherent in a test of multiple analytes, principal components analysis was employed to reduce the acylcarnitines from 45 separate metabolites, into a single "acylcarnitine factor." We then tested for an association between this acylcarnitine factor and multiple indices of physical performance and self-reported function.

Results. The acylcarnitine factor accounted for 40% of the total variance in 45 acylcarnitines. Of the metabolites analyzed, those that contributed most to our one-factor solution were even-numbered medium and long-chain species with side chains containing 10–18 carbons (factor loadings ≥0.70). Odd-numbered chain species, in contrast, had factor loadings 0.50 or less. Acylcarnitine factor scores were inversely related to physical performance as measured by the Short Physical Performance Battery total score, two of its three component scores (gait and chair stands Short Physical Performance Battery), and usual and maximal gait speeds ($\rho = -0.324$, -0.348, -0.309, -0.241, and -0.254, respectively; $p < .05$).

Conclusions. Higher acylcarnitine factor scores were associated with lower levels of objectively measured physical performance in this group of older, largely overweight men. Metabolic profiles of rodents exhibiting lipid-induced mitochondrial dysfunction show a similar phenotypic predominance of medium- and long-chain acylcarnitines.

Key Words: Physical performance—Physical function——Metabolic profiling—Acylcarnitine—Aging.

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ACCORDING to the U.S. Census Bureau, by the year 2030, one of five Americans (about 70 million) will be older than 65 years (1–2) and 86% of all adult Americans will be overweight or obese (3). As Americans live longer and the rate of obesity increases (4), so does the need to better address evolving changes in patient health, especially regarding disorders with a metabolic contributor, such as type 2 diabetes mellitus and cardiovascular disease. Quality-of-life and health outcomes in older adults have been measured traditionally with physical performance batteries and function questionnaires such as the Short Physical Performance Battery (SPPB) and the physical function subscale of the Medical Outcomes Study 36-Item Short-Form Health Survey (SF36-PF) (5–8). However, few investigators have explored the metabolic contributors to these clinically relevant physical performance measures.

Data from both human and rodent studies suggest that abnormalities in metabolically dysregulated states such as obesity and insulin resistance can be detected with assays of small-molecule metabolites in plasma (9–15). For example, we have observed that abnormal levels of plasma acylcarnitines are associated with insulin resistance, coronary artery disease, and incident cardiovascular events (9–15). Also, there is an inverse relationship between circulating

medium-chain acylcarnitines and the glucose disposition index, a measure of pancreatic beta-cell function in the frequently sampled intravenous glucose tolerance test, suggesting that these metabolic intermediates might play a role in the progression to diabetes (9). Shah and colleagues (15) observed a high heritability of circulating plasma small-molecule metabolites, including those from branched-chain amino acids and fatty acids, in premature coronary artery disease, establishing a possible genetic basis for these profiles. The same group has reported that a cluster of circulating short-chain dicarboxylated acylcarnitines is predictive of incident cardiovascular events, even after correction for a broad array of clinical and demographic factors (16).

Carnitine, the carrier moiety of acylcarnitines, plays an essential role in mitochondrial metabolism and muscle bioenergetics (17). Its deficiency, as evidenced in inborn errors of metabolism, results in profound functional impairment. With supplementation, carnitine has been found to reduce total fat mass and increase total muscle mass in the elderly population (18). For younger people, beneficial effects of increased carnitine intake have been documented in training, competition, and recovery from strenuous exercise (19,20). Numerous studies suggest that it reduces physical and mental fatigue (17–24). Despite these positive findings, direct changes in muscle carnitine levels have been inconclusive (17,19,20). Although no negative effects have been reported from increasing dietary carnitine, some studies show no greater benefit in performance or quality of life from exercise training with supplementation than exercise alone (17,19,20). In the current study, we profiled plasma acylcarnitines in a population of elderly men with various degrees of physical performance and function. We sought to determine the association between physical function and plasma metabolites. Elucidation of such relationships might lead to a better understanding of metabolic mechanisms underlying disability in older adults.

Methods

Participants

Participants were previously enrolled in the U.S. Veterans LIFE study. Enrollment procedures, measures, and outcomes have been described elsewhere (25). Briefly, the study was a 12-month randomized trial comparing multi component physical activity counseling to usual primary care with change in gait speed as the primary end point. Participants were aged 70 years or older, not engaged in regular physical activity, and free of the following: terminal diagnosis, unstable angina, history of ventricular tachycardia, chronic obstructive pulmonary disease, uncontrolled hypertension, stroke, active substance abuse, dementia, severe hearing or vision loss, chronic pain, and diagnosis of mental or behavioral disorder. As part of a supplemental analysis, participants of the Veterans LIFE study were invited to return for a 24-month follow-up 1 year after completing the LIFE study. Two hundred thirty-eight individuals returned and 77 consented to participate in this study.

Metabolic Profiling

Blood was collected by venipuncture at 24 months. Ethylenediaminetetraacetic acid plasma samples were stored at −80°C until time of assay. Conventional metabolites were measured using a Hitachi 911 analyzer (26). Reagents were obtained from Roche (Indianapolis, IN; glucose), Wako USA (Richmond, VA; nonesterified fatty acids), and Sigma (St Louis, MO; triglycerides). Forty-five acylcarnitines were measured using a targeted mass spectrometry–based platform as previously described (26).

Principal Components Analysis

Raw values from metabolites were log transformed to better approximate normality. To control for type I error inherent in a test of 45 individual predictors, principal components analysis (PCA), a data reduction technique, was performed to decrease these multiple metabolites into a smaller set of constructed latent variables (principal components or "factors"). These components account for common variance in the original measurements (27). Thus, markers that correlate highly with one another will form common factors. The number of factors retained is typically determined by balancing the variance explained and distribution of factor scores. By convention, each factor score has a mean of 0 and a standard deviation of 1. This statistical technique has been used in prior studies of metabolic intermediates (9,13,15,28). Once PCA was completed and the number of retained components determined, scores on the factor for each of the 77 participants were computed. Each participant's factor score represented his/her level on an optimally weighted sum for that participant's set of acylcarnitine predictors (29).

Physical Performance Measures

Gait speeds were recorded by 8-foot walk time. Standing balance, chair stands, and gait speed were scored categorically from 0 to 4. These scores were then summed to constitute the SPPB, where higher scores reflect better physical performance (30). Grip strength was measured using a hydraulic hand dynamometer (BASELINE) and endurance assessed by 400-m corridor walk (31).

Self-Reported Physical Function, Medical Conditions, and Symptoms

SF36-PF was selected as an indicator of overall health-related quality of life. This survey has good construct validity and has been widely used (32,33). The Late-Life Function (LLF) Index provided a summary score of overall physical function. Its subscales assess the capacity to

Table 1. General Participant Characteristics ($N = 77$ for all measures)

Characteristic	Mean ± *SD*
Demographics	
Age (years)	79.2 ± 4.8
Body mass index (kg/m^2)	28.4 ± 4.1
Self-rated health	
No. of health conditions per participant	5.0 ± 2.4
No. of symptoms per participant	6.1 ± 4.1
Metabolic parameters	
Glucose (mg/dL)	122 ± 41
Nonesterified fatty acids (mmol/L)	0.5 ± 0.3
Triglycerides (mg/dL)	152.4 ± 91.1

complete upper extremity (LLF-UE) tasks, basic lower extremity (LLF-BLE) skills, as well as more advanced lower extremity (LLF-ALE) activities (34). All scales were scored by normalizing raw data to a range of 0–100, with higher scores indicating higher function. Thirteen medical conditions and 19 health-related symptoms were ascertained by questionnaire.

Statistical Analysis

Clinical and demographic measures were described by means ± standard deviations for continuous variables. Spearman correlations were used to determine an association between participant factor scores and physical performance measures (velocity of usual, maximal, and 400-m walk speed and each SPPB item) or physical function scores (SF36-PF, LLF, LLF-UE, LLF-BLE, LLF-ALE). For these associations we controlled for participant age, body mass index, and self-reported presence of circulation problems, diabetes, and arthritis. Statistical significance was declared at $p < 0.05$. All analyses were performed using SAS version 9.1 (SAS Institute Inc., Cary, NC).

Results

General Characteristics and Metabolic Measures

Participants had a mean age of 79.2 ± 4.8 years (range 72–88 years) and a body mass index of 28.4 ± 4.1 kg/m^2 (range 20.8–40.7 kg/m^2). Participants reported 5.0 ± 2.4 medical conditions and 6.1 ± 4.1 health-related symptoms. The most common medical conditions endorsed were hypertension, arthritis, and heart disease. Average glucose concentration was 122 ± 41 mg/dL (range 70–333 mg/dL). Average nonesterified fatty acid concentration was 0.5 ± 0.3 mmol/L and mean triglyceride levels were 152.4 ± 91.1 mg/dL (Table 1).

Principal Components Analysis

In a three-factor model, the eigenvalue and proportion of variance for factors 1, 2, and 3 were 17.97 and 39.94%, 5.12 and 11.37%, and 3.58 and 7.95%, respectively. For parsimony, based on eigenvalue, scree test, and variance, we used only factor 1 in this analysis. We reduced acylcarnitines from 45 separate analytes into a single "acylcarnitine factor" to account for 40% of the total variance. Side chains on the 45 acylcarnitines analyzed by tandem mass spectrometry ranged in size from 2 to 22 carbons. Acylcarnitine species that contributed most to the one-factor solution were medium- and long-chain species whose acyl side chains contained 10–18 carbons (factor loadings ≥0.70). Odd-chain species derived from amino acid catabolism, such as C3s and C5s, contributed very modestly to the one-factor solution (loadings ≤0.50) (Table 2).

Physical Performance and Physical Function Measures

Mean values of objective physical performance measures were above established thresholds of impairment. Grip strength was 31.8 ± 7.0 kg and the SPPB score was 10.1 ± 1.9 (the suggested cutoff for impaired physical performance being 9.0) (35). Walking velocities in a 400-m walk (1.08 ± 0.31 m/s), usual gait speed (1.15 ± 0.29 m/s), and maximal gait speed (1.67 ± 0.45 m/s) were greater than the 1.0 m/s cutoff for physical impairment (8). Self-reported physical function, as measured by the SF36-PF, was 68.1 ± 22.8 (range 10–100), three points above the national average for men aged 65 years and older (33). The normalized averages for LLF (61.4 ± 11.1; range 39–100), LLF-UE (75.9 ± 11.9; range 48–100), LLF-BLE (73.3 ± 15.1; range 45–100), and

Table 2. The Acylcarnitine Factor, a One-Factor Solution by Principal Components Analysis

Metabolites	Description	Factor Loading
C10-OH/C8-DC, C12:1, C14:1-OH/C12:1-DC, C12-OH/C10-DC, C14:1, C12, C14, C14:2, C16:1, C16:2, C8:1-DC, C18:1, C10:1, C2, C18:1-OH/C16:1-DC, C14-OH/C12-DC, C16:1-OH/C14:1-DC, C16	Mainly by-products of beta-oxidation (medium- and long-chain acylcarnitines, ranging from C10 to C18) and acetylcarnitine (C2)	≥0.70
C18:2, C6-DC, C6:1-DC/C8:1-OH, C8:1, C10:2, C4-OH, C10, C10:3, Ci4-DC/C4-DC, C20:1-OH/C18:1-DC, C6, C20, C18		0.51–0.69
C16-OH/C14-DC, C8, C5-OH/C3-DC, C5-DC, C20-OH/C18-DC, C18:2-OH, C18-OH/C16-DC, C3, C5's, C4/Ci4, C7-DC, C22, C20:4, C5:1	By-products of amino acid catabolism (odd-chain acylcarnitines) and long-chain fatty acid oxidation (C16 to C22)	≤0.50

Note: Metabolites are listed in descending order according to their factor load. DC = dicarboxy; OH = hydroxy.

Table 3. Physical Performance Measures and Self-Reported Physical Function ($N = 77$ for all measures)

	Mean ± *SD*
Physical performance measures	
Grip strength (kg)	31.8 ± 7.0
Short Physical Performance Battery (SPPB; range 0–12)	10.1 ± 1.9
SPPB gait (range 0–4)	3.8 ± 0.5
SPPB balance (range 0–4)	3.4 ± 0.9
SPPB chair stands (range 0–4)	2.8 ± 1.2
400-m walk (m/s)	1.08 ± 0.31
Usual gait speed (m/s)	1.15 ± 0.29
Maximal gait speed (m/s)	1.67 ± 0.45
Self-reported physical function	
36-Item physical function subscale (range 0–100)	68.1 ± 22.8
Late-Life Function score (range 0–100)	61.4 ± 11.1
Upper extremity subscale (range 0–100)	75.9 ± 11.9
Basic lower extremity subscale (range 0–100)	73.3 ± 15.1
Advanced lower extremity subscale (range 0–100)	53.3 ± 17.1

LLF-ALE (53.3 ± 17.1; range 0–100) were all at levels indicating only modest functional limitation (see Table 3) (34).

Correlations

Acylcarnitine factor scores were inversely related to physical performance as measured by the SPPB total score and two of its three component scores, gait SPPB and chair stands SPPB (ρ = −0.324, −0.348, and −0.309, respectively; $p < .05$). Similarly, there was a negative association between participant factor scores and physical performance, assessed as usual and maximal gait speeds (ρ = −0.241 and −0.254, respectively; $p < .05$). Factor scores were also inversely related to 400-m walk speed and self-reported SF36-PF, LLF, LLF-UE, LLF-BLE, and LLF-ALE, but these relationships were relatively lower in strength of association. Likewise, participants reporting poorer physical function tended to have higher factor scores (Table 4).

Table 4. Correlations of Acylcarnitine (AC) Factor Scores With Physical Performance Measures and Self-Reported Physical Function*

	Spearman Partial Correlation Coefficients for AC Factor	
	ρ	*p* Value
Physical performance measures		
Short Physical Performance Battery (SPPB)	−0.324	.01†
SPPB gait	−0.348	.003†
SPPB balance	−0.128	.29
SPPB chair stands	−0.309	.01†
400-m walk (m/s)	−0.217	.08
Usual gait speed (m/s)	−0.241	.04†
Maximal gait speed (m/s)	−0.254	.03†
Self-reported physical function		
36-Item physical function subscale	−0.218	.07
Late-Life Function score (normalized total)	−0.195	.10
Upper extremity subscale	−0.049	.68
Basic lower extremity subscale	−0.162	.17
Advanced lower extremity subscale	−0.206	.08

Notes: *Controlling for age, body mass index, and selected health conditions (arthritis, diabetes, problems with circulation in peripheral limbs).
†$p < .05$.

Discussion

In this investigation, we used metabolic profiling to elucidate indicators of physical performance and function. To the best of our knowledge, this is the first study to report an association between circulating plasma acylcarnitines and multiple objective measures of physical performance in elderly men. Here, we used PCA as a data reduction technique for analyzing multiple metabolic intermediates. Our primary end point, using this type of correlation analysis suggests an inverse association between acylcarnitine factor scores and physical performance measures. In addition, the predominant acylcarnitines represented in our one-factor solution were medium- and long-chain species; the same metabolites that have been implicated in lipid-induced mitochondrial dysfunction in rodents (10,14).

Study participants were largely overweight but otherwise healthy community dwellers. Both objective measures of physical performance and self-reports of physical function were above established thresholds for impairment. Their average plasma glucose and lipid levels were grossly within normal limits. Thus, metabolic profiling in this cohort grants an opportunity to seek possible metabolic phenotypes among older men who outwardly appear relatively well functioning, apart from their weight status. We found that higher acylcarnitine factor scores were correlated with lower measures of physical performance.

Metabolic profiling, also known as metabolomics, is emerging as a valuable tool for clinical phenotyping. Our group has particularly focused on "targeted" mass spectrometry–based methods for metabolic profiling that employ stable isotope dilution as a means for quantification of analytes spanning several chemical classes or modules reviewed in Bain and colleagues (36). Among the analyte modules that we have available is the measurement of acylcarnitines of different chain length and degree of saturation by tandem mass spectrometry. It is generally accepted that acylcarnitine levels correspond to the acyl coenzyme A compounds in various mitochondrial metabolic pathways, for example, beta-oxidation, Krebs cycle, and branched-chain amino acid catabolism. For instance, fatty acids are converted into their even-chain acylcarnitines during beta-oxidation, whereas amino acid catabolism generates odd-chain acylcarnitines. Thus, profiling of plasma acylcarnitines affords an assessment of multiple metabolic processes occurring in different tissues at a particular time and can be used as a granular method of phenotyping in the context of multiple clinical diseases and conditions (13,16). Older adults are of particular interest because they often present with numerous diseases at various stages, as evidenced in this study.

The association noted in this study importantly links whole-body assessments of physical performance to molecular processes reflecting mitochondrial function and metabolism. Even-chain acylcarnitines with side chains between 10 and 18 carbons in length were identified as the major contributors to our one-factor solution. Odd-chain acylcarnitines, in contrast, contributed much less. Although outside the purview of this study, we would ideally like to move beyond reporting a metabolic signature.

A recent study of rodents fed a high-fat diet for 12 months showed marked perturbations in mitochondrial fuel metabolism, including fatty acid oxidation (14). When the induction of fatty acid oxidation occurs without a coordinated increase in tricarboxylic acid cycle flux, this leads to incomplete lipid oxidation and an accumulation of acylcarnitine intermediates (10,14). This buildup of acylcarnitines may produce a feedback loop that modulates or signals metabolic stress (10). An essential component of this model would be an available pool of carnitine, the carrier moiety of acylcarnitine. Consistent with this line of reasoning, conditions where carnitine levels may dwindle secondary to decreased nutrition, impaired biosynthesis, or increased expenditure would benefit from supplementation. For instance, patients suffering from cachexia or cirrhosis, or on dialysis, experience some symptom relief with carnitine supplementation (17,20,22,24). Recent studies indicate that supplementation attenuates metabolic stress and muscle damage after hypoxic exercise (17,19,20). Likewise, carnitine supplementation has been thought to upregulate androgen receptors, thereby promoting recovery from resistance exercise (17,19). As mentioned earlier, oral carnitine has been shown to alleviate certain symptoms of aging. Given these findings, the molecular and statistical groundwork laid by our study can lead to interesting future studies evaluating the relationship of dietary medium- and long-chain fatty acids and physical performance in the elderly population.

A major strength of this analysis is the novel finding that links these metabolic analytes to numerous measures of physical performance and function. SPPB gait, SPPB chair stands, and usual and rapid gait speeds all exhibited statistically significant correlations with our acylcarnitine factor scores. We note that the associations observed were highest among measures of mobility, lower extremity function, endurance, and, to a lesser degree, balance and global self-reports of function. It is possible that the metabolic processes observed might be a preclinical indicator of obesity-related musculoskeletal impairment or sarcopenia. Additional studies will be necessary to clarify this observation.

We note several limitations in this study. The study population was restricted to male veterans. Although users of Veterans Affairs health care tend to have more chronic illnesses than their non–Veterans Affairs user counterparts (37), men in general have fewer functional limitations than women. One might speculate that the observations in this study may be more pronounced in women. Furthermore, individuals in this study were participants of the Veterans LIFE study who returned for their 24-month follow-up and consented to venipuncture. A comparison of these 77 follow-up participants with those who did not return showed that our 77 participants were a healthier subset (38). These selection biases would, if anything, tend to underestimate the extent of pathology in the general population and provide valuable biomarker candidates for study of men and women in the United States older than 70 years.

Although physical performance is highly predictive of incident hospitalization and disabling events such as falls and death (7,26,38–40), the molecular correlates underlying these phenomena still remain unclear. The associations found in this study highlight a link between relative levels of a specific plasma metabolite and impaired muscle function. To our knowledge, this study is the first to show a correlation between plasma acylcarnitines and multiple measures of physical performance in elderly men. An important clinical implication is that metabolic dysregulation as reflected by fluctuations in catabolic intermediates can be detected in the peripheral circulation. As such, metabolic profiling may provide a means of identifying an at-risk group of elderly men to target for earlier intervention to prevent future functional decline. The potential utility of metabolic intermediates as biomarkers would depend on recognizing and establishing concentration ranges in individuals of various ages and disease states. Thus, future investigations should include longitudinal measurements of both men and women, and evaluation of the prognostic significance of acylcarnitine factor scores for predicting trajectories of functional decline. This additional information would not only serve to validate findings in our current cross-sectional analysis but may also provide a molecular basis for future interventions in at-risk populations.

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