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Insulin Resistance Is Associated With Reduced Mitochondrial Oxidative Capacity Measured by ^{31}P-Magnetic Resonance Spectroscopy in Participants Without Diabetes From the Baltimore Longitudinal Study of Aging

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PATHOPHYSIOLOGY

Whether individuals with insulin resistance (IR) but without criteria for diabetes exhibit reduced mitochondrial oxidative capacity is unclear; addressing this question could guide research for new therapeutics. We investigated 248 participants without diabetes from the Baltimore Longitudinal Study of Aging (BLSA) to determine whether impaired mitochondrial capacity is associated with prediabetes, IR, and duration and severity of hyperglycemia exposure. Mitochondrial capacity was assessed as the postexercise phosphocreatine recovery time constant (τ_{PCr}) by ^{31}P-magnetic resonance spectroscopy, with higher τ_{PCr} values reflecting reduced capacity. Prediabetes was defined using the American Diabetes Association criteria from fasting and 2-h glucose measurements. IR and sensitivity were calculated using HOMA-IR and Matsuda indices. The duration and severity of hyperglycemia exposure were estimated as the number of years from prediabetes onset and the average oral glucose tolerance test (OGTT) 2-h glucose measurement over previous BLSA visits. Covariates included age, sex, body composition, physical activity, and other confounders. Higher likelihood of prediabetes, higher HOMA-IR, and lower Matsuda index were associated with longer τ_{PCr}. Among 205 participants with previous OGTT data, greater severity and longer duration of hyperglycemia were independently associated with longer τ_{PC}. In conclusion, in individuals without diabetes a more impaired mitochondrial capacity is associated with greater IR and a higher likelihood of prediabetes.

Muscle biopsy specimens showed that individuals with type 2 diabetes have lower muscle mitochondrial content and oxidative capacity, mitochondrial proteins, and expression of oxidative genes than control subjects (1), but findings are inconsistent across studies (2,3), especially when accounting for obesity. Not all of the studies using ^{31}P-magnetic resonance spectroscopy (^{31}P-MRS) confirmed that individuals with type 2 diabetes have impaired mitochondrial function (4). Moreover, similar mitochondrial capacity was found in individuals with early-stage type 2 diabetes and prediabetes compared with normoglycemic control subjects (5,6). Thus, whether insulin resistance (IR) and prediabetes are linked to impaired mitochondrial capacity remains unclear. Inconsistent findings among studies may be due to small sample size, use of different diagnostic criteria, and inadequate adjustment for confounders (Supplementary Table 1).

Using data on ^{31}P-MRS collected in 248 participants without diabetes in the Baltimore Longitudinal Study of Aging (BLSA), we tested whether impaired mitochondrial capacity is associated with prediabetes, IR, and the duration and severity of hyperglycemia exposure.

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RESEARCH DESIGN AND METHODS

Study Design and Setting

BLSA is a study of human aging established in 1958 by the National Institute on Aging Intramural Research Program (7). BLSA continuously enrolls healthy volunteers ≥20 years of age, followed at intervals of 1–4 years, with more frequent follow-up visits for older persons. The study protocol is reviewed by the National Institute of Environmental Health Sciences Institutional Review Board, and participants consent to participate after receiving an extensive description of the study.

Participants

We studied 248 BLSA participants without diabetes, who were 51–97 years old (mean age 73.5 ± 9.6 years, 46.4% men) with available data from ^{31}P-MRS, oral glucose tolerance test (OGTT) results, and confounders. Information on race (Caucasian vs other), smoking (current smoker, former smoker, or no smoking), and physical activity (questionnaire on different activities transformed in metabolic equivalents of resting oxygen consumption) (8) were self-reported. Body weight in kilograms, and height and waist circumference in centimeters were assessed. BMI was calculated as weight/height (kg/m^2). Total body DEXA was performed using the Prodigy Scanner (General Electric) to obtain measures of total body fat mass (TBFM) and trunk fat mass (FM) in kilograms. TBFM was also normalized by body weight and expressed as the percentage of body fatness (i.e., TBFM divided by body weight and multiplied by 100). Serum interleukin-6 (IL-6) and CRP were measured with ELISA (R&D Systems, Minneapolis, MN; and Alpco, Salem, NH, respectively). Plasma leptin level was measured using ELISA (LINCO Research, St. Charles, MO), whereas plasma adiponectin level was measured by radioimmunoassay (LINCO Research).

^{31}P-MRS–Measured Mitochondrial Capacity

^{31}P-MRS measurements of phosphorus-containing metabolites were obtained from the vastus lateralis muscle of the left thigh using a 3-T Achieva MRI scanner (Philips, Best, the Netherlands) and a 10-cm ^{31}P-tuned, flat surface coil (PulseTeq, Surrey, U.K.). Participants performed rapid and intense ballistic knee extensions (9) to maximally recruit quadriceps and rapidly deplete phosphocreatine (PCr) with minimal acidification, which were practiced at least 15 min before starting the actual examination. Exercise duration was controlled to achieve a 33–67% reduction in PCr peak height and never exceeded 42 s, resulting in a postexercise recovery period of 5.8–6.3 min, which was sufficient for reliable fitting of the recovery coefficient. MRI signals were acquired before, during, and after this exercise protocol, with a repetition time of 1.5 s using a pulse-acquire sequence adiabatic radiofrequency excitation over a period of 7.5 min, starting 1 min before exercise to define baseline values, with a time resolution of 6 s (10). Data were analyzed by jMRUI (version 5.0), and metabolites were quantified using a nonlinear least squares algorithm (AMARES), based on the integrated area of the spectral line (11,12). The postexercise PCr recovery time constant (τ_{PCr}) was calculated by fitting the time-dependent recovery of PCr to the monoexponential recovery function, as follows:

$$PCr(t) = PCr_0 + \Delta PCr\left(1 - e^{-t/\tau PCr}\right)$$

where PCr_0 represents the amount of PCr immediately after in-magnet exercise, and ΔPCr is the difference in PCr between baseline and postexercise conditions.

Muscle pH was monitored during the protocol based on the chemical shift difference between inorganic phosphate (Pi) and PCr. Subjects showing pH values of <6.8 were excluded from further analysis (13).

Prediabetes Status and IR

Participants were classified as being "normal," having prediabetes, or having diabetes, according to the American Diabetes Association criteria using fasting plasma glucose (FPG) and/or 2-h post-OGTT glucose (2hG) levels (14). For OGTT, fasting participants consumed 75 g of an oral solution of glucose, and blood samples were collected after fasting and then every 20 min for 2 h. Type 2 diabetes was defined as history of type 2 diabetes and taking hypoglycemic medications; or FPG ≥126 mg/dL and 2hG ≥200 mg/dL at the same visit; or FPG ≥126 mg/dL or 2hG ≥200 mg/dL at consecutive visits. Participants with diabetes were excluded from the current study. Prediabetes was defined as follows: FPG ≥100 mg/dL but <126 mg/dL or 2hG ≥ 140 mg/dL but <200 mg/dL at the same visit; or FPG ≥100 mg/dL but <126 mg/dL or 2hG ≥140 mg/dL but <200 mg/dL during two consecutive visits. IR was estimated by HOMA-IR, calculated as FPG (mg/dL) × fasting insulin (mU/L) divided by 405 (15). Insulin sensitivity was assessed by the Matsuda index (10,000/square root of [(fasting glucose × fasting insulin) × (mean glucose × mean insulin during OGTT)]) (16) and the Reduced Matsuda Index (10,000/square root of [(fasting glucose × fasting insulin) × (glucose at 120 min × insulin at 120 min)]) (17). Duration of hyperglycemia exposure was assessed as the number of years from the onset of prediabetes. Severity of hyperglycemia exposure was estimated for participants with longitudinal data (N = 205) as the average OGTT 2-h glucose level from the time of the first OGTT to mitochondrial capacity assessment.

Statistical Analysis

Variables were summarized as the mean ± SD, median (interquartile range), or number (percentage). The relationships between τ_{PCr} (in seconds) and prediabetes, HOMA index, Matsuda index, and reduced Matsuda index were explored using Spearman correlations. Logistic and linear regression models were fitted to test the associations of mitochondrial oxidative capacity with prediabetes, IR/insulin sensitivity, and the severity and duration of hyperglycemia exposure. Covariates included age, sex and percentage of PCr

depletion (model I); race, education, smoking status, physical activity level, body weight, body height, and DEXA-measured trunk FM (model II); and levels of plasma IL-6, CRP, leptin, and adiponectin (model III [or the fully adjusted model]). Alternative anthropometric and body composition measures were also tested as confounders (model IV–VII). All analyses were performed by the SAS statistical package, version 9.3 (SAS Institute Inc., Cary, NC) and R version 3.1.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

The prevalence of prediabetes was 40.3%. The median time from the onset of diabetes was 14 years. The main characteristics of the population according to prediabetes status are presented in Table 1. τ_{PCr} was significantly higher in subjects with prediabetes compared with normal subjects and according to HOMA tertiles, and was significantly lower according to tertiles of the Matsuda index and reduced Matsuda index (Fig. 1). Independent of all confounders, τ_{PCr} significantly and positively correlated with prediabetes and HOMA, whereas it correlated negatively with the Matsuda index (Supplementary Table 2). Participants with higher τ_{PCr} values were more likely to have prediabetes and to be in a higher tertile of IR (odd ratios >1) and were less likely to be a higher tertile of insulin sensitivity (odd ratios <1) than those with lower τ_{PCr} values (Table 2). Comparing tertiles of τ_{PCr}, both the highest and the medium tertiles were significantly associated with prediabetes and impaired insulin sensitivity compared with the lowest tertiles (Supplementary Table 3).

Relationships of τ_{PCr} with the Matsuda index and the reduced Matsuda index did not depart from linearity (Supplementary Fig. 1), whereas for HOMA-IR a cubic spline provided the best fit (Supplementary Table 4). Using OGTT-based surrogate indices developed by Abdul-Ghani et al. (18), we found that τ_{PCr} was not associated with liver IR, but was inversely and significantly correlated with muscle insulin sensitivity. Adjusting for physical activity and/or

Table 1—Characteristics of the sample population according to prediabetes status

	Normal (*n* = 148)	Prediabetes (*n* = 100)	*P* value
Age (years)	73.3 ± 10.1	73.9 ± 8.9	0.570
Male sex	55 (37.2)	60 (60)	<0.001
Caucasian race	110 (74.3)	69 (69)	0.388
Education (years)	18 (16–18)	17 (16–18)	0.627
Weight (kg)	71.5 ± 13.2	79.1 ± 13.9	<0.001
Height (cm)	165.2 ± 8.2	169.2 ± 9.4	<0.001
BMI (kg/m^2)	26.1 ± 3.8	27.5 ± 3.7	0.005
TBFM (DEXA-measured), kg	23.9 ± 8.7	27.8 ± 9.3	<0.001
Body fatness (TBFM/weight*100), %	33 ± 9	35 ± 9	0.154
Waist circumference (cm)	86.6 ± 11.7	93.5 ± 11.1	<0.001
Trunk FM (kg)	11.05 ± 4.9	14.5 ± 5.3	<0.001
Smokers (former or current)	55 (37.2)	47 (47)	0.148
Physical activity (MET-min/day)	311 (165.5–490.5)	243.0 (133.5–445.0)	0.104
IL-6 (pg/mL)	3.9 (3.1–5)	4 (3.3–5.1)	0.494
CRP (μg/mL)	0.99 (0.47–2.49)	0.95 (0.50–2.50)	0.841
Leptin (ng/mL)	11.3 (5.2–20.6)	11.2 (5.3–19.4)	0.843
Adiponectin (μg/mL)	13.4 (7.7–21.4)	12.7 (5.4–18.4)	0.164
Fasting glucose (mg/dL)	91.1 ± 8.7	102.2 ± 11.6	<0.001
OGTT 2-h glucose (mg/dL)	105.7 ± 26.5	141.8 ± 39.4	<0.001
Homa IR units*	1.31 (0.95–1.76)	1.91 (1.27–2.96)	<0.001
Matsuda index**	5.72 (4.07–7.75)	3.96 (2.59–5.66)	<0.001
Reduced Matsuda index***	7.62 (5.09–10.5)	4.28 (2.77–7.47)	<0.001
Previous BLSA visits with OGTT data (*n*)	3 (2–4)	4 (3–5)	<0.001
Severity of exposure to hyperglycemia (average OGTT 2-h glucose, mg/dL, from previous BLSA visits)	104.2 ± 19.0	134.5 ± 27.5	<0.001
τ_{PCr} (s)	48.9 (42.4–56.8)	53.4 (53.4–47.7)	0.001
%PCr depletion	34.7 (27.7–45.7)	35.2 (27.4–45.1)	0.959

Values are reported as the mean ± SD, *n* (%), or median (interquartile range). *HOMA index (IR) = [fasting glucose (mg/dL) × fasting insulin (mU/L)]/405. **Matsuda index (insulin sensitivity) = 10,000/$\sqrt{}$[(fasting glucose × fasting insulin) × (mean OGTT glucose concentration × mean OGTT insulin concentration). ***Reduced time points − Matsuda index (Reduced Matsuda Index) (insulin sensitivity) = 10,000/$\sqrt{}$[(fasting glucose × fasting insulin) × (OGTT 2-h glucose × OGTT 2-h insulin).

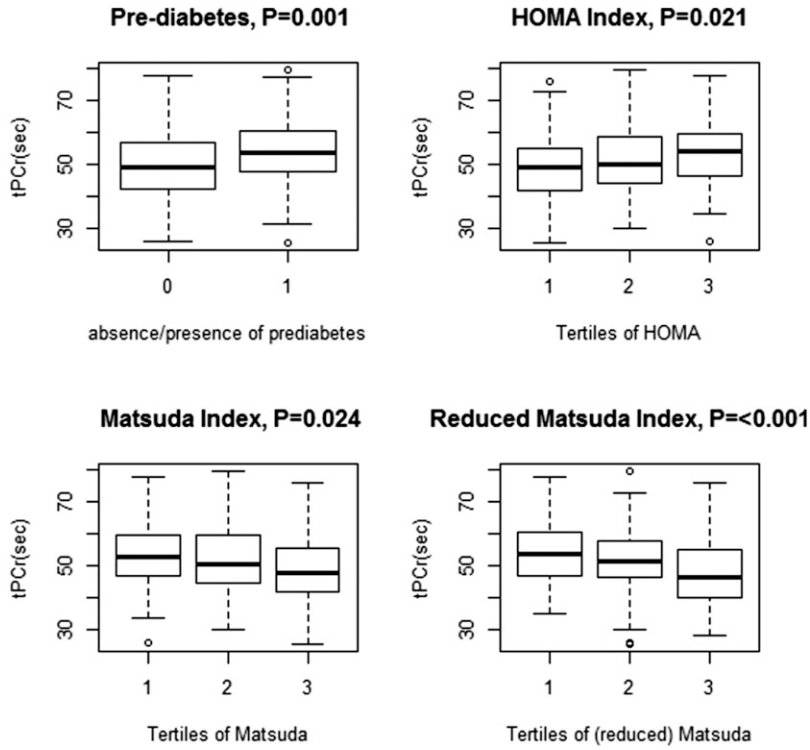

Figure 1— Unadjusted median values and range of τ_{PCr} (in seconds) according to the presence of prediabetes, IR (HOMA index), and insulin sensitivity (Matsuda index and reduced Matsuda index).

trunk FM, the association was attenuated and no longer significant (Supplementary Table 5).

Adjusting for confounders, and greater severity and longer duration of hyperglycemia exposure, even when both were included as predictors in the same model, were independently associated with greater mitochondrial impairment (Table 3).

DISCUSSION

Using data from 248 BLSA participants with diabetes, we examined the relationship between IR and ^{31}P-MRS–measured mitochondrial oxidative capacity. Independent of confounders, a larger τ_{PCr} value was significantly associated with a higher likelihood of having prediabetes, more severe HOMA-IR, and lower insulin sensitivity (Matsuda index). The severity and duration of hyperglycemia exposure were independently associated with larger τ_{PCr} values.

Time course studies in rodents suggest that mitochondrial impairment follows diet-induced diabetes (3). However, human studies showed mitochondrial impairment in insulin-resistant offspring of patients with types 2 diabetes, suggesting that impaired oxidative capacity may drive IR (19). Weight loss has no effect on mitochondrial capacity (20), but Coen et al. (21) recently found that exercise superimposed on bariatric surgery enhances mitochondrial respiration and improves insulin sensitivity in patients with severe obesity. Similarly, exercise in overweight-to-obese older adults improves insulin sensitivity and increases muscle oxidative capacity (1), perhaps by enhancing mitochondrial biogenesis. Of note, prolonged exercise training can, at least in part, reverse mitochondrial impairment associated with a long-standing diabetic state (6).

Our study suggests that mitochondrial impairment occurs before IR progression to type 2 diabetes. Consistently, in a small group of older adults who did not have diabetes but had IR, a significant reduction in ^{31}P-nuclear magnetic resonance saturation transfer (ST)–measured muscle phosphorylation activity was found compared with young control subjects (22). Our study further supports these findings in a larger and better characterized sample population, accounting for the potential confounding variables of body composition and physical inactivity, and demonstrating the independent association of both the severity and duration of hyperglycemia with reduced mitochondrial capacity. Noteworthy, ST is a technique that allows measurement of the ATP synthesis rate at rest and minimizes the variability of exercise. The postexercise PCr synthesis used in our study expresses the capacity to respond to an energetic challenge and may be more sensitive to even minor metabolic derangements than ST (1).

The mechanism by which mitochondrial impairments could lead to IR is unclear. In impaired mitochondria, the flux of electrons in the electron transport chain is impaired, and spare electrons are more likely to leak in the mitochondrial matrix and produce radical oxygen species. The resulting oxidative stress may further damage mitochondria and affect IR directly or indirectly by triggering a local inflammatory response (4). It also is possible that hyperglycemia plays a key

Table 2—Results from multivariate logistic models testing the association between τ_{PCr} (s) and likelihood (odds ratio) of having prediabetes or being in a higher tertile of HOMA index, Matsuda index, and reduced Matsuda index

	Likelihood of prediabetes											
	Model I (age, sex, and %PCr depletion adjusted) (*N* = 248)			Model II* (*N* = 248)			Model III§ (*N* = 248)					
	OR (95% CI)		*P* value	OR (95% CI)		*P* value	OR (95% CI)		*P* value			
τ_{PCr} (s)	1.05 (1.03–1.08)		<0.001	1.06 (1.02–1.09)		<0.001	1.06 (1.03–1.10)		<0.001			
	Model IV† (*N* = 247)			Model V# (*N* = 248)			Model VI** (*N* = 248)			Model VII‡ (*N* = 248)		
	OR (95% CI)	*P* value		OR (95% CI)	*P* value		OR (95% CI)	*P* value		OR (95% CI)	*P* value	
τ_{PCr} (s)	1.07 (1.03–1.10)	<0.001		1.06 (1.03–1.09)	<0.001		1.05 (1.02–1.09)	<0.001		1.06 (1.03–1.09)	<0.001	
	Higher tertile of HOMA index (IR)											
	Model I (age, sex, and %PCr depletion adjusted) (*N* = 248)			Model II* (*N* = 248)			Model III§ (*N* = 248)					
	OR (95% CI)		*P* value	OR (95% CI)		*P* value	OR (95% CI)		*P* value			
τ_{PCr} (s)	1.04 (1.01–1.06)		0.002	1.04 (1.01–1.07)		0.002	1.04 (1.01–1.07)		0.003			
	Model IV† (*N* = 247)			Model V# (*N* = 248)			Model VI** (*N* = 248)			Model VII‡ (*N* = 248)		
	OR (95% CI)	*P* value		OR (95% CI)	*P* value		OR (95% CI)	*P* value		OR (95% CI)	*P* value	
τ_{PCr} (s)	1.05 (1.02–1.08)	0.001		1.04 (1.01–1.07)	0.003		1.03 (1.01–1.06)	0.015		1.05 (1.02–1.08)	0.001	
	Higher tertile of Matsuda index (insulin sensitivity)											
	Model I (age, sex, and %PCr depletion adjusted) (*N* = 248)			Model II* (*N* = 248)			Model III§ (*N* = 248)					
	OR (95% CI)		*P* value	OR (95% CI)		*P* value	OR (95% CI)		*P* value			
τ_{PCr} (s)	0.96 (0.94–0.98)		0.001	0.96 (0.93–0.99)		0.004	0.96 (0.93–0.99)		0.003			
	Model IV† (*N* = 247)			Model V# (*N* = 248)			Model VI** (*N* = 248)			Model VII‡ (*N* = 248)		
	OR (95% CI)	*P* value		OR (95% CI)	*P* value		OR (95% CI)	*P* value		OR (95% CI)	*P* value	
τ_{PCr} (s)	0.95 (0.92–0.98)	0.001		0.96 (0.93–0.98)	0.003		0.97 (0.94–0.99)	0.011		0.95 (0.93–0.98)	0.001	
	Higher tertile of reduced Matsuda index (insulin sensitivity)											
	Model I (age, sex, and %PCr depletion adjusted) (*N* = 248)			Model II* (*N* = 248)			Model III§ (*N* = 248)					
	OR (95% CI)		*P* value	OR (95% CI)		*P* value	OR (95% CI)		*P* value			
τ_{PCr} (s)	0.95 (0.93–0.97)		<0.001	0.95 (0.92–0.98)		<0.001	0.95 (0.92–0.98)		<0.001			
	Model IV† (*N* = 247)			Model V# (*N* = 248)			Model VI** (*N* = 248)			Model VII‡ (*N* = 248)		
	OR (95% CI)	*P* value		OR (95% CI)	*P* value		OR (95% CI)	*P* value		OR (95% CI)	*P* value	
τ_{PCr} (s)	0.94 (0.92–0.97)	<0.001		0.95 (0.92–0.98)	<0.001		0.96 (0.93–0.98)	0.001		0.95 (0.92–0.97)	<0.001	

OR, odds ratio. *Age, sex, %PCr depletion, race, education, smoking status, physical activity level, body weight, body height, and DEXA-measured trunk FM. §Age, sex, %PCr depletion, race, education, smoking status, physical activity level, body weight, body height, DEXA-measured trunk FM, and plasma levels of IL-6, CRP, leptin, and adiponectin. †Age, sex, %PCr depletion, race, education, smoking status, physical activity level, body height, body weight, waist circumference, and plasma levels of IL-6, CRP, leptin, and adiponectin. #Age, sex, %PCr depletion, race, education, smoking status, physical activity level, body weight, body height, DEXA-measured TBFM, and plasma levels of IL-6, CRP, leptin, and adiponectin. **Age, sex, %PCr depletion, race, education, smoking status, physical activity level, body height, percentage of body fatness, and plasma levels of IL-6, CRP, leptin, and adiponectin. ‡Age, sex, %PCr depletion, race, education, smoking status, physical activity level, BMI, and plasma levels of IL-6, CRP, leptin, and adiponectin.

Table 3—Results from multivariate regression models testing the association between τ_{PCr} and severity (average OGTT 2-h glucose, in mg/dL, from previous BLSA visits) and/or duration (years from the onset of prediabetes) of hyperglycemia exposure (both included as predictors in the same model)

	τ_{PCr}					
	Model I (age, sex, and %PCr depletion adjusted) (*N* = 205)		Model II* (*N* = 205)		Model III§ (*N* = 205)	
	β (SE)	*P* value	β (SE)	*P* value	β (SE)	*P* value
Severity of hyperglycemia exposure (mg/dL)	0.05 (0.03)	0.042	0.05 (0.03)	0.059	0.05 (0.03)	0.055
Duration of hyperglycemia exposure (years)	0.16 (0.07)	0.019	0.16 (0.07)	0.019	0.16 (0.07)	0.023

	Model IV† (*N* = 204)		Model V# (*N* = 205)		Model VI‡ (*N* = 205)		Model VII** (*N* = 205)	
	β (SE)	*P* value	β (SE)	*P* value	β (SE)	*P* value	β (SE)	*P* value
Severity of hyperglycemia exposure (mg/dL)	0.06 (0.03)	0.026	0.05 (0.03)	0.051	0.05 (0.03)	0.064	0.06 (0.03)	0.034
Duration of hyperglycemia exposure (years)	0.17 (0.07)	0.013	0.14 (0.07)	0.037	0.15 (0.07)	0.028	0.16 (0.06)	0.017

Participants with available longitudinal data on OGTT from previous visits were 205 in 248. *Age, sex, %PCr depletion, race, education, smoking status, physical activity level, body weight, body height, DEXA-measured trunk FM. §Age, sex, %PCr depletion, race, education, smoking status, physical activity level, body weight, body height, DEXA-measured trunk FM, and plasma levels of IL-6, CRP, leptin, and adiponectin. †Age, sex, %PCr depletion, race, education, smoking status, physical activity level, body height, body weight, waist circumference, and plasma levels of IL-6, CRP, leptin, and adiponectin. #Age, sex, %PCr depletion, race, education, smoking status, physical activity level, body weight, body height, DEXA-measured TBFM, and plasma levels of IL-6, CRP, leptin, and adiponectin. ‡Age, sex, %PCr depletion, race, education, smoking status, physical activity level, body height, percentage of body fatness, and plasma levels of IL-6, CRP, leptin, and adiponectin. **Age, sex, %PCr depletion, race, education, smoking status, physical activity level, BMI, and plasma levels of IL-6, CRP, leptin, and adiponectin.

role in mitochondrial impairment. Patients with well-controlled type 2 diabetes have diminished muscle ATP synthesis despite normal glucose transport/phosphorylation (23). In addition, ^{31}P-nuclear magnetic resonance ST–measured mitochondrial activity correlates positively with insulin sensitivity and negatively with insulin secretion, suggesting that reduced insulin signaling might limit mitochondrial oxidative rates (24). Also, mitochondrial activity negatively correlates with hepatic lipid content, supporting a link between altered muscle and liver energy metabolism in promoting IR (24). However, short-term elevation of plasma lipid levels does not affect ATP synthase in human skeletal muscle, suggesting that lipid-induced IR is unlikely to be due to a direct effect of lipid species on mitochondrial function (25).

A major limitation of our study is the cross-sectional design. Hyperinsulinemic-euglycemic clamp would have been more accurate and robust than surrogate indices to evaluate insulin sensitivity, but is time consuming and difficult to perform in large epidemiological studies (18), like the BLSA. Moreover, the severity of hyperglycemia exposure was estimated from OGTT 2-h glucose levels rather than from fasting glucose levels, but the fasting glucose level predominantly reflects liver IR, rather than muscle IR. Also, the severity of hyperglycemia exposure was based on different lengths of follow-up across participants, but we accounted for that in the analysis. Furthermore, we could not investigate race differences in mitochondrial function since BLSA participants are mostly Caucasian. Objective measurements of physical activity by accelerometers would have been more accurate than self-reports, but the accelerometer was recently introduced in the BLSA and was not available for the current sample. Finally, investigating the relationship between mitochondrial function and intramyocellular lipid content would be interesting, but these data are still unavailable in the BLSA.

Despite limitations, our study suggests that reduced mitochondrial oxidative capacity is an integral part of the IR in adult and older persons, and should be considered a possible therapeutic target to reduce the consequences of this condition and prevent progression to type 2 diabetes.

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