Insulin Resistance Is Associated With Decreased Quadriceps Muscle Strength in Nondiabetic Adults Aged ≥70 Years

JOSHUA I. BARZILAY, MD[1]
GEORGE A. COTSONIS, MS[2]
JEREMY WALSTON, MD[3]
ANN V. SCHWARTZ, PHD[4]
SUZANNE SATTERFIELD, MD, DRPH[5]
IVA MILJKOVIC, MD, PHD[6]
TAMARA B. HARRIS, MD[7]
FOR THE HEALTH ABC STUDY

OBJECTIVE — Lower-limb muscle strength is reduced in many people with diabetes. In this study, we examined whether quadriceps muscle strength is reduced in relation to insulin resistance in well-functioning ambulatory nondiabetic individuals.

RESEARCH DESIGN AND METHODS — Participants (age ≥70 years) underwent dual-energy X-ray absorptiometry (DEXA) scanning to ascertain muscle and fat mass, tests of quadriceps strength, computed tomography scanning of the quadriceps to gauge muscle lipid content, and fasting insulin and glucose level measurements from which homeostasis model assessment of insulin resistance (HOMA-IR) was derived.

RESULTS — In regression analysis, quadriceps strength per kilogram of muscle mass was negatively associated ($P < 0.0001$) with HOMA-IR independent of other factors negatively associated with strength such as increased age, female sex, low-physical activity, impaired fasting glucose, and increased total body fat. Muscle lipid content was not associated with strength.

CONCLUSIONS — A small decrease in quadriceps muscle force is associated with increased HOMA-IR in well-functioning nondiabetic adults, suggesting that diminished quadriceps muscle strength begins before diabetes.

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In a recent analysis of the Cardiovascular Health Study, an observational study of cardiovascular disease risk factors in people aged ≥65 years, insulin resistance was found to predict frailty in nondiabetic individuals (1). Frailty in that study was defined, in part, by slowness of gait and low exercise tolerance, both of which characterize lower-limb muscle weakness. At follow-up, individuals who were found to have developed frailty were also twice as likely to have developed new-onset diabetes as those who did not develop frailty. From these results, it is possible to hypothesize that diminished lower-limb strength is related to insulin resistance.

In this study, we conducted a cross-sectional analysis of a nondiabetic healthy cohort from the Health, Aging, and Body Composition (Health ABC) Study to examine whether decreased quadriceps muscle strength is associated with insulin resistance. The analysis accounts for factors that affect muscle function, such as inflammation and muscle fat, and for factors associated with insulin resistance, such as fat mass and physical activity.

From [1]Kaiser Permanente of Georgia and the Division of Endocrinology, Emory University School of Medicine, Atlanta, Georgia; the [2]Department of Biostatistics, Rollins School of Public Health, Emory University, Atlanta, Georgia; the [3]Department of Geriatrics, Johns Hopkins Medical Institutions, Baltimore, Maryland; the [4]Department of Epidemiology and Biostatistics, University of California San Francisco, San Francisco, California; the [5]Department of Preventive Medicine, University of Tennessee Health Science Center, Memphis, Tennessee; the [6]Center for Aging and Population Health, University of Pittsburgh, Pittsburgh, Pennsylvania; and the [7]Geriatric Epidemiology Section, Laboratory of Epidemiology, Demography, and Biometry, National Institute on Aging, Bethesda, Maryland.
Corresponding author: Joshua Barzilay, Joshua.barzilay@kp.org.
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RESEARCH DESIGN AND METHODS — The Health ABC Study is an ongoing prospective cohort study of older adults that examines declines in physical functioning in relation to measures and changes in body composition (2). The present study cohort consists of 2,006 well-functioning adults (age 70–79 years) who self-reported no difficulty with walking one-quarter mile or walking up 10 steps without stopping, who underwent dual-energy X-ray absorptiometry (DEXA) and computed tomography scans, who had fasting blood testing for glucose, insulin, and inflammation factor levels, and who do not have diabetes (use of hypoglycemic agents and/or a fasting glucose level >125 mg/dl). Lean quadriceps muscle mass was derived from DEXA scanning (2). Axial computed tomography scans at the mid-thigh level were done to obtain the mean attenuation coefficient of the quadriceps muscle, an indicator of muscle fat infiltration (2). Quadriceps strength was measured using an isokinetic dynamometer (Kin-Com dynamometer, 125 AP) for knee extension. Maximal voluntary concentric isokinetic torque was assessed in newton meters (3). Insulin resistance was calculated using the homeostasis model assessment (HOMA): fasting glucose × fasting insulin level/22.5 (4), a validated measure of insulin resistance (5).

Pearson's correlation was used to investigate the association of HOMA of insulin resistance (HOMA-IR) with quadriceps strength, mass, and strength per kilogram of muscle mass. Linear regression was done to examine the relationship of quadriceps strength per kilogram of muscle mass with HOMA-IR with adjustment for age, activity level, total body fat, race, sex, quadriceps attenuation coefficient, and presence of impaired fasting glucose (IFG).

RESULTS — There were no statistically significant differences across HOMA-IR quartiles with regard to age, sex, height, current smoking, race, and statin use, as well as A1C, interleukin-6, and tumor necrosis factor levels. Subjects with higher HOMA-IR values were

Table 1—*Pearson's correlation coefficients of quadriceps strength, quadriceps muscle mass, and strength normalized for muscle mass with HOMA-IR in nondiabetic Health ABC participants*

	Male		Female		
	White	Black	White	Black	Overall
n	650	311	600	418	
Quadriceps strength (Nm)	0.015 (0.702)	−0.017 (0.765)	0.008 (0.852)	−0.005 (0.924)	0.017 (0.467)
Quadriceps mass (kg)	0.164* (<0.001)	0.165* (0.002)	0.237* (<0.001)	0.194* (<0.001)	0.189* (<0.001)
Quadriceps strength per kilogram of muscle mass (Nm/kg)	−0.110* (0.007)	−0.141* (0.019)	−0.135* (0.002)	−0.124* (0.016)	−0.089* (<0.001)

Data are Pearson's *r* (*P*). *Statistically significant.

heavier, had higher total body fat mass, and had higher insulin and fasting glucose levels compared with those in subjects with lower scores. Groups did not differ with regard to chronic disease prevalence or energy expenditure, with the exception of higher creatinine levels and lower energy expenditure in the highest quartile of HOMA-IR.

Correlation coefficients of quadriceps strength, mass, and strength per kilogram of muscle mass with HOMA-IR can be found in Table 1. There was no significant association between quadriceps strength and HOMA-IR; however, there was a significant association of quadriceps muscle mass with HOMA-IR. Strength per kilogram of muscle mass was negatively associated with HOMA-IR. There were 9 and 13% differences in mean quadriceps strength per kilogram of muscle mass between women and men in the lowest HOMA-IR quartile (women: 12.66 ± 4.66; men: 19.97 ± 7.48 Nm/kg) and women and men in the highest HOMA-IR quartile (women: 10.95 ± 3.85; men: 17.40 ± 5.94 Nm/kg), respectively.

Linear regression modeling of quadriceps strength per kilogram of muscle mass showed a strong negative relationship with HOMA-IR ($P < 0.001$). Increased age ($P < 0.0001$) and total body fat ($P < 0.0001$), IFG ($P = 0.006$), female sex ($P < 0.0001$), and decreased activity level ($P = 0.016$) were also negatively associated with quadriceps strength per kilogram of muscle mass. The quadriceps attenuation coefficient was not significantly associated with strength. Thirty-one percent of strength variation was accounted for in this model.

CONCLUSIONS— In the present study, the evidence shows that mildly diminished quadriceps muscle strength per kilogram of muscle mass is associated with increased HOMA-IR in ambulatory well-functioning adults without diabetes. This association is independent of total body fat mass, level of physical activity, increased age, IFG, and quadriceps muscle fat content. Even though these cross-sectional findings cannot be used to impute a causal association, they do suggest that diminished quadriceps strength and insulin resistance are related. Because the participants in this study reported no ambulatory impairments, the observed decreases in quadriceps strength are subclinical. This conclusion is consistent with prior Health ABC analyses, which showed that people with diabetes (a stage of illness that follows insulin resistance) had more subclinical functional limitations in the lower extremities than people without diabetes (6). It should be noted that the Health ABC Study does not have a measure of participant fitness ($V\text{O}_{2\text{max}}$), so we are unable to adjust our findings for this important covariate that is also related to insulin resistance/sensitivity (7).

Our results are consistent with the effects of insulin on muscle function. Insulin helps regulate protein metabolism in muscle. In vitro studies (8) show that insulin stimulates the production of muscle proteins. In vivo studies (9) suggest that the effect of insulin on muscle is to prevent muscle protein breakdown. There is an age-related decrease in response to insulin (10) that is likely related to declines in insulin receptor substrate-1 function (11). Other studies of muscle tissue suggest that mitochondrial proteins influenced by insulin are impaired with aging (12).

Our results support the hypothesis that relatively small decreases in quadriceps muscle strength may be related to insulin resistance in older adults, in addition to other well-established factors such as increased fat mass or decreased physical activity (13). In this regard, the Diabetes Prevention Program showed that the greatest reduction in progression to diabetes in people with insulin resistance was in older adults who exercised (14). Likewise, a study by Nair and colleagues (15) demonstrated that older adults who exercised more than 1 h per day had insulin sensitivity similar to trained younger adults. A prospective analysis of the Health ABC Study is planned to test whether quadriceps strength independently predicts increases in glucose levels.

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