INSULIN RESISTANCE IS ASSOCIATED WITH DECREASED QUADRICEPS MUSCLE STRENGTH IN NON-DIABETIC ADULTS, AGE ≥ 70 YEARS

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**Objective:** Lower limb muscle strength is reduced in many people with diabetes mellitus (DM). In this study, we examined whether quadriceps muscle strength is reduced in relation to insulin resistance (IR) in well-functioning ambulatory non-diabetic individuals.

**Research Design:** Participants, age ≥70 years, underwent DEXA scanning to ascertain muscle and fat mass; tests of quadriceps strength; CT scanning of the quadriceps to gauge muscle lipid content; and fasting insulin and glucose levels from which HOMA-IR was derived.

**Results:** In regression analysis, quadriceps strength per kilogram muscle mass was negatively associated (p<0.0001) with HOMA-IR independent of other factors negatively associated with strength – increased age, female gender, 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 non-diabetic adults, suggesting that diminished quadriceps muscle strength begins prior to DM.
In a recent analysis of the Cardiovascular Health Study—an observational study of cardiovascular disease risk factors in people ≥65 years - insulin resistance (IR) was found to predict frailty in non-diabetic 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. Individuals who developed frailty were also twice as likely to develop new-onset diabetes mellitus (DM) during follow up as those who did not develop frailty. From these results it may be hypothesized that diminished lower limb strength is related to IR.

In this study we conduct a cross-sectional analysis of a non-diabetic healthy cohort from the Health, Aging and Body Composition (Health ABC) study to examine whether decreased quadriceps muscle strength is associated with IR. Analyses accounts for factors that affect muscle function, such as inflammation and muscle fat, and for factors that associate with IR, such as fat mass and physical activity.

**METHODS**

The Health ABC study is an ongoing prospective cohort study of older adults which examines declines in physical functioning in relation to measures and changes in body composition (2). The present study cohort consists of 2006 well-functioning adults, ages 70-79 years, who self-reported no difficulty walking ¼ mile or walking up 10 steps without stopping, and who underwent a DEXA scan, a CT scan, had fasting blood testing for glucose, insulin, and inflammation factor levels, and who do not have DM (use of hypoglycemic agents and/or a fasting glucose level >125 mg/dl). Lean quadriceps muscle mass was derived from DEXA scanning (2). Axial CT 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 (N-m) (3). IR was calculated using the homeostasis model assessment (HOMA): (fasting glucose x fasting insulin level / 22.2) (4), a validated measure of IR (5).

Pearson correlation was used to investigate the association of HOMA-IR with quadriceps strength, mass, and strength per kg mass. Linear regression was done to examine the relationship of quadriceps strength per kg muscle mass with HOMA-IR with adjustment for age, activity level, total body fat, race, gender, 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, statin use, nor HbA1c, interleukin-6, and tumor necrosis factor levels. Those with higher HOMA-IR values were heavier, had higher total body fat mass, and higher insulin and fasting glucose levels than those 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 kg muscle mass with HOMA-IR appear in the Table. There was no significant association between quadriceps strength and HOMA-IR. There was, however, a significant association of quadriceps muscle mass with HOMA-IR. Strength per kg muscle mass was negatively
associated with HOMA-IR. There was a 9% and 13% difference in mean quadriceps strength per kg muscle mass, respectively, among women and men between those in the lowest (female: 12.66±4.66; male: 19.97±7.48) and highest (female: 10.95±3.85; male: 17.40±5.94 N-m/kg) HOMA-IR quartiles.

Linear regression modeling of quadriceps strength per kg 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 gender (p<0.0001), and decreased activity level (p=0.016) were also negatively associated with quadriceps strength per kg muscle mass. The quadriceps attenuation coefficient was not significantly associated with strength. 31% of strength variation was accounted for in this model.

DISCUSSION

In the present study, evidence is presented that mildly diminished quadriceps muscle strength per kilogram muscle mass is associated with increased HOMA-IR in ambulatory well-functioning adults without DM. 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 IR are related. Since the participants in this study reported no ambulatory impairments, the observed decreases in quadriceps strength are sub-clinical. This conclusion is consistent with prior Health ABC analyses that showed that people with DM (a stage of illness that follows IR) had more sub-clinical functional limitations in the lower extremity than people without DM (6). It should be noted, that Health ABC does not have a measure of participant fitness (VO2 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 (8) studies 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) which 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 IR 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 DM in people with IR was in older adults who exercised (14). Likewise, a study by Nair (15) demonstrated that older adults who exercised >1 hour per day had insulin sensitivity similar to trained younger adults. A prospective analysis of Health ABC is planned to test whether quadriceps strength independently predicts increases in glucose levels.

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BIBLIOGRAPHY

1. Barzilay JI, Blaum C, Moore T, Xue QL, Hirsch CH, Walston JD, Fried LP. Insulin resistance and inflammation as precursors of frailty: The Cardiovascular Health Study. Arch Intern Med 167: 635 – 641, 2007
2. Goodpaster BH, Carlson CL, Visser M, Kelley DE, Scherzinger A, Harris TB, Stamm E, Newman AB. Attenuation of skeletal muscle and strength in the elderly: The Health ABC Study. J Appl Physiol 90: 2157–2165, 2001
3. Newman AB, Haggerty CL, Goodpaster B, Harris T, Kritchevsky S, Nevitt M, Miles TP, Visser M; Health Aging And Body Composition Research Group. Strength and muscle quality in a well-functioning cohort of older adults: The Health, Aging and Body Composition Study. J Am Geriatr Soc 51: 323 – 330, 2003
4. Wallace TM, Levy JC, Matthews DR. Use and abuse of HOMA modeling. Diabetes Care 27: 1487 – 1495, 2004
5. Bonora E, Targher G, Alberiche M, Bonadonna RC, Saggiani F, Zenere MB, Monauini T, Muggeo M. Homeostasis model assessment closely mirrors the glucose clamp technique in the assessment of insulin sensitivity: studies in subjects with various degrees of glucose tolerance and insulin sensitivity. Diabetes Care 23: 57 – 63, 2000
6. de Rekeneire N, Resnick HE, Schwartz AV, Shorr RL, Kuller LH, Simonsick EM, Vellas B, Harris TB. Diabetes is associated with subclinical functional limitation in nondisabled older individuals: The Health, Aging, and Body Composition study. Diabetes Care 26:3257-3263, 2003
7. Messier V, Malita FM, Rabasa-Lhoret R, Brochu M, Karelis AD. Association of cardiorespiratory fitness with insulin sensitivity in overweight and obese postmenopausal women: a Montreal Ottawa New Emerging Team study. Metabolism 57:1293-1298, 2008
8. Fulks RM, Li JB, Goldberg AL. Effects of insulin, glucose, and amino acids on protein turnover in rat diaphragm. J Biol Chem 250: 290 – 298, 1975
9. Gelfand RA, Barrett EJ. Effect of physiologic hyperinsulinemia on skeletal muscle protein synthesis and breakdown in man. J Clin Invest 80: 1 – 6, 1987
10. Fink RI, Revers RR, Kolterman OG, Olefsky JM. The metabolic clearance of insulin and the feedback inhibition of insulin secretion are altered with aging. Diabetes 34: 275 – 280, 1985
11. White MF. IRS proteins and the common path to diabetes. Am J Physiol Endocrinol Metab 283:E413-E422, 2002
12. Petersen KF, Befroy D, Dufour S, Dziura J, Ariyan C, Rothman DL, DiPietro L, Cline GW, Shulman GI. Mitochondrial dysfunction in the elderly: possible role in insulin resistance. Science 300: 1140 – 1142, 2003
13. Cheng YJ, Gregg EW, De Rekeneire N, Williams DE, Imperatore G, Caspersen CJ, Kahn HS. Muscle-strengthening activity and its association with insulin sensitivity. Diabetes Care 30: 2264-2270, 2007
14. Diabetes Prevention Program Research Group, Crandall J, Schade D, Ma Y, Fujimoto WY, Barrett-Connor E, Fowler S, Dagogo-Jack S, Andres R. The influence of age on the effects of lifestyle modification and metformin in prevention of diabetes. J Gerontol A Biol Sci Med Sci 61:1075-1081, 2006
15. Lanza IR, Short DK, Short KR, Rakhavakimal S, Basu R, Joyner MJ, McConnell JP, Nair KS. Endurance training as a countermeasure for aging. Diabetes 57: 2933 – 2942, 2008
Table: Pearson correlation coefficients of quadriceps strength, quadriceps muscle mass, and strength normalized for muscle mass with HOMA-IR in non-diabetic Health ABC participants. Numbers in parentheses are p values. Highlighted numbers are statistically significant.

|                          | Male               | Female              | Overall             |
|--------------------------|--------------------|---------------------|---------------------|
|                          | White N=650        | Black N=311         | White N=600         | Black N=418         |
| Race                     |                    |                     |                     |                     |
|                          |                    |                     |                     |                     |
| Quadriceps strength (N-m)| 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 Kg Muscle Mass (N-m/kg) | **-0.110** (0.007) | **-0.141** (0.019)  | **-0.135** (0.002)  | **-0.124** (0.016)  | **-0.089** (<0.001) |