Accelerated Loss of Skeletal Muscle Strength in Older Adults With Type 2 Diabetes

The Health, Aging, and Body Composition Study

SEOK WON PARK, MD, DRPH[1,2]
BRET H. GOODPASTER, PHD[3]
ELSA S. STROTMEYER, PHD[2]
LEWIS H. KULLER, MD, DRPH[2]
ROBERT BROUDEAU, PHD[2]
CANDACE KAMMERER, PHD[4]
NATHALIE DE REKENEIRE, MD[5]
TAMARA B. HARRIS, MD[6]
ANN V. SCHWARTZ, PHD[7]
FRANCES A. TYLAVSKY, PHD[8]
YONG-WOOK CHO, MD[1]
ANNE B. NEWMAN, MD, MPH[2]
FOR THE HEALTH, AGING, AND BODY COMPOSITION STUDY

OBJECTIVE — It has been shown that adults with either long-standing type 1 or type 2 diabetes had lower skeletal muscle strength than nondiabetic adults in cross-sectional studies. The aim of the study was to investigate longitudinal changes of muscle mass and strength in community-dwelling older adults with and without type 2 diabetes.

RESEARCH DESIGN AND METHODS — We examined leg and arm muscle mass and strength at baseline and 3 years later in 1,840 older adults aged 70–79 years in the Health, Aging, and Body Composition Study. Regional muscle mass was measured by dual energy X-ray absorptiometry, and muscle strength was measured using isokinetic and isometric dynamometers.

RESULTS — Older adults with type 2 diabetes ($n = 305$) showed greater declines in the leg muscle mass (-0.29 ± 0.03 vs. -0.23 ± 0.01 kg, $P < 0.05$) and strength (-16.5 ± 1.2 vs. -12.4 ± 0.5 Nm, $P = 0.001$) compared with older adults without diabetes. Leg muscle quality, expressed as maximal strength per unit of muscle mass (Newton meters per kilogram), also declined more rapidly in older adults with diabetes (-1.6 ± 0.2 vs. -1.2 ± 0.1 Nm/kg, $P < 0.05$). Changes in arm muscle strength and quality were not different between those with and without diabetes. Rapid declines in leg muscle strength and quality were attenuated but remained significant after controlling for demographics, body composition, physical activity, combined chronic diseases, interleukin-6, and tumor necrosis factor-α.

CONCLUSIONS — In older adults, type 2 diabetes is associated with accelerated loss of leg muscle strength and quality.

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From the [1]Department of Internal Medicine, Pochon CHA University, Pochon, Korea; the [2]Department of Epidemiology, University of Pittsburgh, Pittsburgh, Pennsylvania; the [3]Department of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania; the [4]Department of Human Genetics, University of Pittsburgh, Pittsburgh, Pennsylvania; the [5]Division of Diabetes Translation, Centers for Disease Control and Prevention, Atlanta, Georgia; the [6]Laboratory for Epidemiology, Demography and Biometry, National Institute on Aging, Bethesda, Maryland; the [7]Department of Epidemiology and Biostatistics, University of California, San Francisco, California; and the [8]Department of Preventive Medicine, University of Tennessee, Memphis, Tennessee.

Address correspondence and reprint requests to Seok Won Park, MD, DrPH, Department of Internal Medicine, Pochon CHA University, 351 Yatap-dong, Sungnam, 463-712, Korea. E-mail: spark@cha.ac.kr.

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Abbreviations: Health ABC, Health, Aging, and Body Composition Study; IL-6, interleukin-6; TNF-α, tumor necrosis factor-α.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

In industrialized countries, the major increase in the number of people with diabetes is attributed to the aging of the population (1,2). In older adults, diabetes is associated with a two- to threefold increased risk of injurious falls (3) and physical disability (4–8). Several factors have been identified as contributors to diabetes-related disability including obesity (4,5), coronary heart disease (4,5,7), stroke (4), arthritis (4,5), depression (7), and visual impairments (4,5), but still a large portion of the diabetes-disability relationship is not explained by these factors. Alterations in muscular function in diabetes, which can be a potential pathway, have not yet been explored.

Muscle weakness in diabetes has been considered a rare manifestation associated with severe diabetic neuropathy (9). However, recent studies using quantitative assessments of muscular function showed that skeletal muscle strength, especially in the lower extremity, is generally lower in adults with diabetes than in nondiabetic subjects (10–12). The Health, Aging, and Body Composition Study (Health ABC) was designed to investigate the impact of changes in body composition and health conditions on age-related physiological and functional status among adults from 70 to 79 years of age. In this cohort, we have reported that older adults with type 2 diabetes had lower skeletal muscle strength and quality (12). However, it is still unclear whether lower muscle strength in diabetes is a consequence of diabetes or just a coincidence because previous studies were cross-sectional observations. To address this question, we reexamined knee extensor and hand grip strength and body composition 3 years after the initial examination in the Health ABC Study. We hypothesized that older adults with type 2 diabetes would show a greater decline in skeletal muscle strength and quality than older adults without diabetes.

RESEARCH DESIGN AND METHODS

— The Health ABC Study included well-functioning, community-dwelling older adults aged 70–79 years. The Health ABC Study was described in detail elsewhere (12). Among 2,618 participants who had completed baseline assessments for skeletal muscle mass and strength, 1,840 (70.3%) were reexamined 3 years later. The reasons for not having follow-up data were death ($n = 146$), development of disability and/or institutionalization ($n = 302$), missed contact ($n = 77$), withdrawal of the participants ($n = 11$), inability to perform a knee strength test ($n = 191$), and missing data on body composition ($n = 51$). All participants provided informed consent before participating in the study. The consent forms and study protocols were approved by the institutional review boards at each field center.

Diabetes assessment

Participants were considered to have type 2 diabetes if they had *1*) a report of having the diagnosis of diabetes with onset after age 25 and/or *2*) current use of oral hypoglycemic medications or insulin, or *3*) a fasting plasma glucose concentration ≥7.0 mmol/l at baseline. Plasma glucose was measured using an automated glucose oxidase reaction (Vitros 950 analyzer; Johnson & Johnson, Rochester, NY), and A1C was measured by an enzymatic method (Bio-Rad, Hercules, CA).

Body composition

Lean masses of the upper and lower extremities and the total body were assessed using dual-energy X-ray absorptiometry (QDR 4500, software version 8.21; Hologic, Bedford, MA). The validity and reproducibility of the body composition data in the Health ABC Study may be found elsewhere (13,14). Quality assurance measures included the use of a body composition phantom for calibration and annual assessment for potential site differences or drift over time.

Strength assessments

Strength was measured using an isokinetic dynamometer (125 AP; Kin-Com, Chattanooga, TN) for knee extension and isometric dynamometer (Jaymar; JLW Instruments, Chicago, IL) for hand grip strength. For knee extension, maximal voluntary concentric isokinetic torque was assessed in Newton meters at an angular velocity of 60°/s. At least three, but no more than six, maximal efforts were allowed to produce three overlying curves, and the mean maximal torque was recorded and used for the analysis. The right leg was used unless contraindicated by pain or history of joint replacement. For validation of the knee strength assessments, we performed a reliability study in 63 participants. The interexaminer coefficient of variation (CV) was 4.85% with no significant differences between examiners. The intraparticipant CV was 10.68%, and the CV for combined effect of examiner and participant was 11.73%.

Isometric grip strength was assessed for each hand. Participants with severe hand pain or recent surgery were excluded. The vast majority of participants (96%) who had leg strength testing also had grip strength testing. For these analyses, we used the maximum of the force from two trials for the right upper extremity. A measure of muscle quality (leg-specific torque [Newton meters per kilogram] and arm-specific force [kilograms per kilogram]) was created by taking the ratio of strength to the entire corresponding leg or arm muscle mass in kilograms measured by dual-energy X-ray absorptiometry.

Other covariates

Sociodemographic characteristics included age, sex, race, and education. Combined chronic diseases such as coronary heart disease, congestive heart failure, stroke, peripheral artery disease, knee osteoarthritis, depression, and cancer were identified by self-report and confirmed by treatment and medication use. Self-reported poor eyesight was considered as impaired vision. Renal insufficiency was defined by serum creatinine level >1.5 mg/dl in men and 1.2 mg/dl in women (15). The ankle-arm index was calculated, and subclinical peripheral artery disease was defined by ankle-arm index <0.9. Health-related behaviors including smoking, alcohol drinking, and level of physical activity (kilocalories per week) were determined by using a standardized questionnaire (16). Interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) were measured in duplicate using an ultrasensitive enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, MN). The lower limit of detection was <0.10 pg/ml for IL-6 and 0.18 pg/ml for TNF-α, with CVs of 6.3 and 16.0%, respectively.

Statistical analyses

Baseline characteristics of the cohort are presented separately for those with and without diabetes. χ^2 tests were calculated for categorical variables, and a Student's *t* test was used for continuous variables to test for any statistical differences between the two groups. Longitudinal changes of muscle strength and quality were calculated in both absolute terms and relative terms (percent change from baseline). Differences between older adults with and without diabetes were assessed by general linear models controlling for sex, race, age, and clinic site (model 1). Additional adjustments were made for BMI, baseline strength or quality, changes in muscle mass, and physical activity (model 2), plus combined chronic diseases and diabetes-related complications (model 3) and inflammatory cytokines (log-transformed IL-6 and TNF-α in model 4). $P < 0.05$ was accepted as statistically significant. All of the analyses were performed using SPSS software (version 12.0.0; SPSS, Chicago, IL).

RESULTS

— Among the 1,840 older adults with complete assessments of baseline and follow-up skeletal muscle mass and strength tests, 305 (16.6%) had type 2 diabetes at baseline. Older adults with type 2 diabetes were more likely to be men and black and to have a lower level of education (Table 1). Those with diabetes had greater body weight, BMI, and total fat mass as well as higher total lean mass than their nondiabetic counterparts. As expected, combined chronic conditions such as coronary heart disease, peripheral artery disease, impaired vision, and renal insufficiency were more prevalent in those with type 2 diabetes. IL-6 and TNF-α levels were significantly higher in older adults with diabetes (Table 1).

Both diabetic and nondiabetic older adults lost significant amounts of initial muscle strength in 3 years. However, older adults with type 2 diabetes lost their knee extensor strength more rapidly than those without diabetes ($P = 0.001$) (Table 2). Older adults with type 2 diabetes also lost greater amounts of leg lean mass than those without diabetes ($P < 0.05$). Furthermore, muscle quality (maximal strength per unit of muscle mass in Newton meters per kilogram) declined more rapidly in older adults with type 2 diabetes ($P < 0.05$). When expressed in relative changes, older adults with type 2 diabetes showed ~50% more rapid declines in knee extensor strength (−9.0 vs. −13.5%, $P = 0.002$) and muscle

Table 1—*Characteristics of participants by baseline diabetes status in the Health ABC Study*

	Without diabetes	With diabetes	*P* value*
n	1,535	305	
Sociodemographic			
Age (years)	73.4 ± 2.8	73.5 ± 2.7	0.772
Men (%)	47.7	59.1	<0.001
Blacks (%)	32.7	51.9	<0.001
Education <12 years (%)	19.8	30.9	<0.001
Anthropometric (body composition)			
Height (cm)	166.6 ± 9.2	167.0 ± 9.3	0.312
Weight (kg)	75.2 ± 14.4	81.0 ± 14.1	<0.001
BMI (kg/m^2)	27.1 ± 4.4	29.0 ± 4.4	<0.001
Total body fat (%)	33.6 ± 7.6	34.3 ± 7.4	0.050
Total fat mass (kg)	25.5 ± 8.0	27.9 ± 8.2	<0.001
Total lean mass (kg)	47.5 ± 10.1	50.7 ± 9.9	<0.001
Chronic diseases (%)			
Coronary heart disease	15.2	23.7	<0.001
Congestive heart failure	1.5	2.9	0.094
Stroke	1.8	1.9	0.860
PAD	3.0	5.8	0.014
Knee osteoarthritis	8.4	6.8	0.347
Depression	11.6	9.7	0.337
Cancer	21.0	16.6	0.079
Impaired vision	16.7	25.7	<0.001
Renal insufficiency	6.0	11.5	0.001
Subclinical PAD†	9.5	19.1	<0.001
Behavioral factors			
Current smoking (%)	8.5	6.5	0.243
Alcohol drinking (%)	55.4	38.3	<0.001
Physical activity (kcal/week)‡	548 (119–1,446)	403 (57–1,235)	0.024
Biochemical			
Fasting glucose (mmol/l)	5.2 ± 0.5	8.4 ± 2.9	<0.001
A1C (%)	6.0 ± 0.5	7.9 ± 1.6	<0.001
IL-6 (pg/ml)‡	1.63 (1.12–2.44)	2.16 (1.47–3.08)	<0.001
TNF-α (pg/ml)†	3.03 (2.35–3.86)	3.41 (2.57–4.37)	<0.001

Data are means ± SD, proportions, or median (interquartile range). **P* values are from age/sex/race-adjusted logistic regression or linear models comparing participants with and without diabetes. †Subclinical peripheral artery disease (PAD) was defined as ankle-arm index <0.9. ‡Wilcoxon rank-sum test for comparison of medians.

quality (−6.2 vs. −10.0%, $P = 0.01$) in 3 years than those without diabetes. However, the changes in hand grip strength and arm muscle quality were not different between those with and without diabetes although older adults with diabetes lost greater amounts of arm muscle mass (Table 2). There was no indication of an interaction effect ($P < 0.10$) of sex or race with diabetes on the changes in muscle strength or muscle quality.

Table 3 presents the changes in knee extensor strength and muscle quality with controls for potential confounders. A greater decline of knee extensor strength in older adults with type 2 diabetes was not changed by adjustments for sex, race, age, clinic site, BMI, baseline strength, changes in leg muscle mass, and physical activity (models 1 and 2). The association of diabetes and loss of knee extensor strength was slightly attenuated by additional adjustments for combined chronic diseases and inflammatory cytokines (models 3 and 4).

A greater decline of leg muscle quality in older adults with type 2 diabetes was also evident, even after adjustments for demographics, BMI, baseline muscle quality, changes in leg lean mass, and physical activity ($P = 0.001$, model 2). Further adjustments for combined chronic diseases and inflammatory cytokines attenuated the association of diabetes and declines in muscle quality. However, the greater declines in muscle strength and quality in older adults with type 2 diabetes remained significant throughout the adjustment models (Table 3).

CONCLUSIONS — In this study, older adults with type 2 diabetes lost 13.5% of their knee extensor strength, whereas those without diabetes lost 9.0% of initial strength in 3 years. An ~50% more rapid decline in the knee extensor strength in older adults with diabetes was not accounted for by a greater loss of leg muscle mass. Muscle quality also declined more rapidly in older adults with type 2 diabetes, suggesting that diabetes may result in functional impairments in muscular function of the lower extremities, not necessarily accompanied by loss of muscle mass.

Sarcopenia, a status of decreased skeletal muscle mass, is commonly observed in older adults as a result of age-related loss of muscle mass (17–21). In general, it is frequently accompanied by lower skeletal muscle strength. However, determinants or risk factors for sarcopenia and low muscle strength in older adults have not been well identified (22). This is the first epidemiological study showing that type 2 diabetes is associated with rapid loss of skeletal muscle mass and strength in older adults. It confirms the previous cross-sectional finding of lower muscle strength in individuals with diabetes (10–12). It is also consistent with the finding of Andreassen et al. (23) who showed a rapid decline in ankle strength in patients with symptomatic diabetic neuropathy. The findings of this longitudinal study strongly suggest that low muscle strength in adults with type 2 diabetes is a consequence of rather than just a coincidence with type 2 diabetes.

We found discordance between the upper and lower extremities for diabetes and changes in muscle strength. A relative preservation of upper extremity strength has been observed in the process of aging (21,24). Our findings are, in fact, consistent with previous cross-sectional studies showing decreased skeletal muscle strength at the ankle and knee but not at the wrist and elbow in patients with type 2 diabetes (10). Andersen et al. (11) reported that upper extremity strength was preserved even in long-standing type 1 diabetic patients. They also found that muscle strength was related to the presence and severity of peripheral neuropathy in both type 1 and type 2 diabetic patients (10,11). It is well known that the

Table 2—*Three-year changes in skeletal muscle strength, mass, and quality by baseline diabetes status in the Health ABC Study*

	Without diabetes			With diabetes			
	Baseline	36 months	Change	Baseline	36 months	Change	*P* value*
n		1,535			305		
Knee extensor							
Maximal torque (Nm)	109.1 ± 0.7	96.8 ± 0.7	−12.4 ± 0.5†	111.3 ± 1.5	94.8 ± 1.5	−16.5 ± 1.2‡	0.001
Leg lean mass (kg)	7.52 ± 0.03	7.29 ± 0.03	−0.23 ± 0.01‡	7.96 ± 0.07†	7.66 ± 0.07†	−0.29 ± 0.03‡	0.035
Specific torque (Nm/kg)	14.4 ± 0.1	13.2 ± 0.1	−1.2 ± 0.1‡	14.0 ± 0.2†	12.4 ± 0.2†	−1.6 ± 0.2‡	0.034
Hand grip							
Maximal force (kg)	32.6 ± 0.2	31.3 ± 0.2	−1.3 ± 0.1‡	32.1 ± 0.4	30.8 ± 0.4	−1.3 ± 0.3‡	0.964
Arm lean mass (kg)	2.75 ± 0.01	2.70 ± 0.01	−0.06 ± 0.01‡	2.92 ± 0.03†	2.83 ± 0.03†	−0.08 ± 0.01‡	0.025
Specific force (kg/kg)	12.0 ± 0.1	11.8 ± 0.1	−0.2 ± 0.1‡	11.2 ± 0.1†	11.0 ± 0.1†	−0.2 ± 0.1	0.757

Data are adjusted means ± SE from linear models controlling for age, sex, race, and clinic site. **P* values for comparison of 3-year changes between two groups. †$P < 0.01$ versus those without diabetes at the same time period. ‡$P < 0.001$ between baseline and 36 months within the same group.

lower extremities are predominantly involved in diabetic neuropathy presumably because of a length-dependent degeneration of nerve fibers (25,26). If neuropathy is a factor, skeletal muscle function is more likely to be affected in the lower extremities than in the upper extremities.

The exclusion of many participants for follow-up knee extensor strength test may have potentially biased the results to the null because proportionally more subjects with diabetes were excluded because of high mortality and other reasons (see Table 1 of the online appendix, available at http://dx.doi.org/10.2337/dc06-2537). We identified 47 participants with diabetes and 181 without diabetes who were excluded from the knee strength test but had the grip strength test at the follow-up examination. Among them, declines in hand grip strength were greater in older adults with diabetes than in those without diabetes (−3.3 ± 6.7 vs. −1.1 ± 6.2 kg, $P < 0.05$), suggesting that strict criteria for knee strength testing might select stronger individuals and actually obscure the true declines in muscle strength, particularly in those with diabetes (see Table 2 of the online appendix).

Lower extremity strength is essential for maintaining basic physical function, especially mobility such as walking and climbing stairs. It is well known that lower knee extensor strength is associated with an increased risk of incident mobility limitations (27–29). Although it is unclear whether there is a certain threshold level of leg strength to maintain physical function, lower muscle strength is definitely a risk factor for physical disability, independent of lower muscle mass itself (29).

Several studies suggested that the combination of sarcopenia and obesity ("sarcopenic obesity") was more strongly associated with disability than either body composition type alone (30,31). It is possible that the rapid decline in muscle strength in older adults with type 2 diabetes may be associated with sarcopenic obesity. However, to our knowledge there is no study examining the changes in muscle strength in relation to sarcopenic obesity.

The mechanisms for the rapid loss of skeletal muscle strength, in older adults with diabetes are not known. Neuropathic processes involving motor neurons could affect muscle strength, as evidenced by the close association of muscle strength and severity of diabetic neuropathy in the previous cross-sectional observations (10,11). Electrophysiological studies showed that muscle strength in diabetic patients correlated with fiber density and amplitude of the macromotor unit potential, suggesting incomplete reinnervation after axonal loss (32). Longitudinal studies suggest an average loss of compound muscle action potential amplitude at a rate of ~3%/year in patients with type 2 diabetes over a 10-year period (33). Further research should identify the role of the decrease in motor amplitudes on skeletal muscle strength and quality in subjects with diabetes.

In our study, adjustments for comorbid conditions such as cardiovascular disease, stroke, congestive heart failure, peripheral arterial disease, depression, impaired vision, and renal insufficiency slightly attenuated the declines in muscle strength. These results suggest that

Table 3—*Adjusted 3-year changes in knee extensor strength and muscle quality by baseline diabetes status in the Health ABC Study*

	Without diabetes	With diabetes	*P* value
n	1,535	305	
Muscle strength (maximal torque, Nm)			
Model 1	−12.4 ± 0.5	−16.5 ± 1.2	0.001
Model 2	−12.5 ± 0.5	−16.2 ± 1.1	0.001
Model 3	−12.5 ± 0.5	−15.7 ± 1.1	0.008
Model 4	−12.7 ± 0.5	−15.6 ± 1.2	0.026
Muscle quality (specific torque, Nm/kg)			
Model 1	−1.22 ± 0.07	−1.57 ± 0.15	0.034
Model 2	−1.20 ± 0.06	−1.69 ± 0.14	0.001
Model 3	−1.21 ± 0.06	−1.64 ± 0.14	0.006
Model 4	−1.24 ± 0.06	−1.64 ± 0.15	0.018

Data are adjusted means ± SE. Model 1: adjusted for sex, race, age, and clinic site. Model 2: additionally adjusted for BMI, baseline strength or quality, changes in leg lean mass, and physical activity. Model 3: additionally adjusted for coronary heart disease, stroke, congestive heart failure, peripheral artery disease, knee osteoarthritis, cancer, depression, impaired vision, renal insufficiency, and subclinical peripheral artery disease (ankle arm index <0.9). Model 4: additionally adjusted for cytokines (log-transformed IL-6 and TNF-α).

chronic complications of diabetes have a limited role in declines in skeletal muscle strength in older adults with diabetes. However, we had no reliable assessment of nerve function in our study at baseline. It is possible that declines in muscle function may indeed be the result of diabetic neuropathy (23).

Another potential mechanism is increased levels of inflammatory cytokines in subjects with diabetes. It has been reported that systemic inflammatory cytokines such as TNF-α and IL-6 have detrimental effects on muscle mass, strength, and physical performance in older adults (34,35). In our study, rapid declines in muscle strength and quality in older adults with diabetes are attenuated, albeit still significant, after adjusting for IL-6 and TNF-α. These findings may suggest a potential role of inflammatory cytokines on the muscular function in diabetes.

Our study has several limitations. The study participants were well-functioning, community-dwelling older adults who were relatively healthier than other individuals in the typical population of the same age. There were many dropouts, and only ~70% of participants completed follow-up assessments. However, we believe that the loss to follow-up may produce an underestimation of the true decline in muscle function in those with diabetes (see Tables 1 and 2 of the online appendix). The questionnaire to assess physical activity in the Health ABC Study has not been validated in older diabetic subjects. It may not be sensitive enough to detect the influence of different physical activity level on the changes in muscle strength and quality in our study. We also lacked information about neuropathy at baseline, which would be related with muscular function in those with type 2 diabetes.

In summary, the present study demonstrates an accelerated loss of knee extensor strength and quality in older adults with type 2 diabetes.

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