THE IMPACT OF DIABETES MELLITUS ON SKELETAL MUSCLE MASS AND STRENGTH IN OLDER ADULTS

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In older adults, diabetes is a serious public health problem because of high prevalence as well as its devastating consequences such as functional disability and high mortality. Loss of muscle mass and strength, called sarcopenia, has been considered as a common pathway leading to loss of function and frailty in older adults. We investigated the impact of diabetes on skeletal muscle mass and strength in 3,075 older adults aged 70 to 79, enrolled in the Health, Aging and Body Composition Study. Diabetes was defined not only by self report or medication use, but also by fasting plasma glucose and the result of 75-g oral glucose challenge test. Muscle mass was measured by state of the art techniques such as dual-energy X-ray absorptiometry (DXA) and computed tomography (CT). Muscle strength was assessed quantitatively by isometric and isokinetic dynamometers. Muscle quality was defined as maximal muscle strength per unit muscle mass. In cross-sectional study, we found that muscle strength was significantly lower in men with diabetes and not higher in women with diabetes despite of having greater muscle mass than those without diabetes. Muscle quality was consistently lower in both men and women with diabetes than non-diabetic counterparts in both upper and lower extremities. We also found that longer duration ($\geq$ 6 yrs) and poor glycemic control (A1c > 8.0 %) were associated with even lower muscle quality. In longitudinal study, older adults with diabetes showed about 50% greater declines in leg muscle strength compared with those without diabetes. Leg muscle quality also

declined more rapidly in older adults with diabetes. Skeletal muscle mass, estimated by DXA, declined more rapidly in older adults with diabetes. Interestingly, loss of muscle mass was more pronounced in undiagnosed diabetes. Thigh muscle area by CT declined two times faster in older women with either diagnosed or undiagnosed diabetes than non-diabetic women. The public health importance of these findings is that diabetes is clearly a risk factor for loss of muscle mass and strength in older adults. We need to develop a strategy to prevent rapid loss of muscle mass and strength in this high risk population.

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1. INTRODUCTION

1.1 SPECIFIC AIMS

Sarcopenia, a loss of skeletal muscle mass, is commonly observed in older adults. [1-4] Loss of skeletal muscle strength is also one of typical changes with aging. [5-7] Previous studies have demonstrated that low muscle mass and decreased muscle strength is associated with devastating processes in elderly such as functional limitations, [8-10] physical disability, [11-14] falls, [15] loss of independence, [16] and mortality. [17-22] However, the risk factors or determinants for loss of muscle mass and strength in older adults are not fully understood. Advanced age, male sex, and black race are some of known factors associated with sarcopenia. [4, 23] Many chronic health conditions, such as cardiovascular disease, diabetes, osteoarthritis, and kidney failure, are potential risk factors of sarcopenia and need to be elucidated.

Deterioration of glucose metabolism is another common characteristic related to aging process. [24-28] Healthy older adults have higher glucose levels during oral glucose tolerance tests, as well as delayed glucose disappearance during intravenous glucose tolerance tests, than do young healthy subjects. [29] Not only does the prevalence of diabetes mellitus increase with age, but also the incidence rate of new cases increases in people older than the age of 65 years. [30] Diabetes in older adults has been shown to be associated with two- to three fold increased risk of physical limitations and disability. [31-35] However, the impact of diabetes mellitus on the skeletal muscle mass and strength in older adults are largely unknown.

The Health, Aging, and Body Composition (Health ABC) Study is a large on-going epidemiologic study of well-functioning community-dwelling black and white older men and women. The Health ABC Study was designed to investigate the relationship between changes in body composition and functional decline with aging. This cohort is ideally suited to study the cross-sectional association of diabetes with muscle mass and strength, as well as longitudinal impact of diabetes on the changes in muscle mass and strength. We hypothesize that older adults with diabetes will show lower skeletal muscle strength and/or lower muscle quality defined by maximal strength per unit muscle mass. In addition, we hypothesize that older adults with diabetes will show accelerated loss of skeletal muscle mass, strength, and muscle quality than non-diabetic older adults.

This is a cross-sectional and longitudinal study to examine the impact of diabetes mellitus on the skeletal muscle quantity and quality in older adults to achieve the following scientific objectives:

1. To assess whether older adults with diabetes have lower skeletal muscle strength and/or lower muscle quality.
2. To determine the impact of diabetes on the longitudinal changes in skeletal muscle mass and strength, thus establish a temporal relationship between diabetes and muscle mass and strength.
3. To investigate potential dose-response relationship between diabetes mellitus and changes in muscle mass and strength by examining the cumulative effects by duration of exposure (duration of diabetes) and by severity of exposure (glycosylated hemoglobin as an indicator of diabetes severity).

1.2 BACKGROUND AND SIGNIFICANCE

1.2.1 Epidemiology of diabetes mellitus in older adults

1.2.1.1 Prevalence

The prevalence of diabetes mellitus is continuously increasing in the United States as well as in the world. [24-27] There are 14.7 millions of people with diagnosed diabetes in U.S. in year 2004. [30] This number has been doubled during the past 10 years. The major contribution to the rapidly increasing burden of diabetes is the aging population. In 1998, 12.7% of persons aged 70 and older had a diagnosis of diabetes. [27] The age specific prevalence of diabetes is the highest in adults aged 65 to 74, followed by age 75 and older, and age 45 to 64. There are also large numbers of older adults, almost 11% of the U.S. population aged 60 to 74, with undiagnosed diabetes. In the Health ABC Study, approximately one-third of all older people with diabetes remains undiagnosed. [28] If undiagnosed diabetes is combined with previously diagnosed diabetes, about one in five older adults aged 65 and older will have diabetes. Not only the prevalence, but also the incidence rate of diabetes increases in people older than the age of 65 years. In 2004, the incidence of diagnosed diabetes was over five times higher among adults aged 65-79 years (14.9 per 1000 population) than adults less than 45 years of age (2.9 per 1000 population). [30] From 1997 through 2004, the incidence of diagnosed diabetes increased in all the age groups examined. Incidence increased 45% among persons aged 18-44 years (from 2.0 to 2.9 per 1000 population), increased 34% among persons aged 45-64 years (from 8.5 to 11.4 per 1000 population), and increased 43% among persons aged 65-79 years (from 10.4 to 14.9 per 1000 population). Furthermore, it is estimated that adults aged 65 and older will make up most of the diabetic population in the next 25 years. Particularly, adults aged 75 and older will consist of one third of all diabetes population by year 2050. [27]

1.2.1.2 Morbidity and mortality

Older persons with diabetes have higher rates of premature death, functional disability, and coexisting illnesses such as hypertension, coronary heart disease, and stroke. [31-35] Mortality in adults with diabetes is about 2 times higher in men and 3 times higher in women than adults without diabetes. [36-37] The high mortality in adults with diabetes is mainly attributable to the increased risk of death from ischemic heart disease, cerebrovascular disease, and infectious diseases. Mortality ratio in adults with diabetes is about 1.8 to 3.3. [37] In older adults, diabetes is associated with a 2- to 3- fold increased risk of physical disability. [31-35] Physical disability is one of under-appreciated complications of diabetes, besides cognitive disorders, falls, fractures and other geriatric syndromes. [38] Among 5 million older adults with diabetes, 1.2 million or one quarter are unable to do major physical tasks such as walking one quarter of a mile, climbing 10 stairs, or doing housework. 2.5 million or one half have some difficulty doing these tasks. [31] Diabetes is also associated with subclinical functional limitation in community dwelling well functioning older adults in the Health ABC Study. [34] However, the mechanism for impaired physical function in diabetes has been poorly understood. Chronic conditions frequently combined with diabetes such as coronary heart disease, peripheral artery disease, visual impairment, and depression partially explained the association but still 40 % of excess risk for physical disability remained unexplained. [32] In 2002, a total cost of 132 billion dollars are attributable to diabetes including 92 billion dollars for direct medical costs and 40 billion dollars of indirect costs related to disability, work loss, and premature mortality. [39]

1.2.2 Skeletal muscle mass and strength in older adults

Adequate skeletal muscle mass and strength is a crucial component to maintain physical function, mobility and vitality in old age. [8-14] Sarcopenia is a term used to describe the age-associated loss of skeletal muscle mass, although the definition is still unclear. [1-3] Baumgartner, et al. [1] defined sarcopenia as appendicular skeletal muscle mass/height-squared (aLM/ht^2 in kg/m^2) being less than two standard deviations below the mean of a young reference group. Prevalence of sarcopenia increased from 13-24% in persons under 70 years of age to above 50% in persons over 80 years of age in New Mexico Study. [1] However, Baumgartner's method (aLM/ ht^2) was less sensitive to detect sarcopenia in woman and overweight or obese individuals. Newman, et al. [3] used appendicular lean mass adjusted for height and body fat mass by residuals and it was more strongly associated with lower extremity functional limitations (odds ratio=1.9, 95% CI=1.4-2.5) in the Health ABC Study.

In general, skeletal muscle strength declines with increasing age beginning at age 40 to 50. [40-54] Muscle strength of older adults aged 70 and older is about 60 % of the strength of young adults. In other words, people lose about 40% of their muscle strength with aging. Even greater decline of strength more than 50% has been observed for people in their nineties. Typically, the rate of strength decline was reported to be 12 to 15% per decade in cross-sectional studies (Table 1). [23, 40-50] However, it is likely that previous cross-sectional studies underestimated the true age-related decreases in muscle strength because stronger persons may have had a better chance to survive to old age and to be examined in baseline cross-sectional comparisons (survival effect bias). Indeed, longitudinal studies have reported greater declines of muscle strength around 2-3% per year (Table 2). [55-58] Previous studies also reported greater declines of muscle strength in lower extremities than upper extremities. (Table 1 and 2)

Table 1. Selected studies of age related changes in skeletal muscle strength (cross-sectional studies)

Author, Year [Reference]	Age	Sex	N	Results	Comments
Larsson L, 1979 [40]	11 - 70 yrs	M	114	Strength peaked at age 33-34 yr, remained stable to the 40-49 yr, and then decreased by 26 – 38 %.	Descriptive study, Eight age groups Muscle biopsy showed a lower proportion of type II fibers with age.
Murray MP, 1980 [41]	20 - 86 yrs	M	72	Strength of the men in the older age groups was significantly less than that of the youngest group (55% of young men)	Comparisons between three age groups
Murray MP, 1985 [42]	20 - 86 yrs	F	72	Strength of the oldest group ranged from 56 to 78% of that in the youngest group, depending on knee joint position.	Comparisons between three age groups
Young A, 1985 [43]	70s vs 20s	M	24	The mean isometric strength of the quadriceps muscles of 12 healthy men in their seventies was 39% less than that of 12 healthy men in their twenties.	Comparison between two groups
Young A, 1984 [44]	70s vs 20s	F	50	The older women were 35% weaker than the young women and their quadriceps cross-sectional area was 33% .	Comparison between two groups
Vandervoort AA, 1990 [45]	70s vs 20s	F	52	Elderly women had significantly lower peak and average torque values in all comparisons with the young female group (25 to 54% lower)	Comparison between two groups
Overend TJ, 1992 [46]	70s vs 20s	M	25	Compared to the young men, elderly men had significantly smaller quadriceps muscles and were weaker (22-32%) in knee flexion and knee extension.	Comparison between two groups
Poulin MJ, 1992 [47]	60s vs 20s	M	24	Compared to young men, older men had lower concentric peak torque values for knee (32%) extensors.	Comparison between two groups
Lindle RS, 1997 [48]	20-93 yrs	M F	346 308	Both men and women exhibited age-related declines in knee extensor strength starting in the fourth decade at a rate of ~8-10% per decade (a 33% declines in men and 35% declines in women).	Regression analysis Muscle quality (MQ: strength/thigh FFM) was defined. MQ declined with aging.
Lynch NA, 1999 [49]	19 – 93 yrs	M F	364 339	Both genders exhibited an age-related decline in leg muscle quality by ~ 40%, the rate of decline was similar for men and women.	Regression analysis
Metter EJ, 1999 [50, 51]	20 – 90 yrs	M F	353 322	Muscle strength of older adults (aged 80s) was about 60 % of 20 year olds in both men and women. Muscle quality declined with age.	Regression analysis
Newman AB, 2003 [23]	70 - 79	M F	3075	Decline in leg strength: -1.9 ~ -2.1%/yr Decline in arm strength: -1.1 ~ -1.5%/yr	Whites and blacks Muscle quality declined: -1%/yr

Table 2. Selected studies of age related changes in skeletal muscle strength (Longitudinal studies)

Author, Year [Reference]	Age	Sex	N	Results	Comments
Aniansson A, 1992 [55]	Mean: 69 yr	M	9	Muscle strength for knee extension declined by 25-35% over 11-yr period. (2-3%/yr) Histology showed a reduction of type IIb fibers with increase in fiber area.	Only men 11 yr follow-up Final age: 80.4 yrs old
Rantanen T, 1998 [56]	45 - 68	M	3,741	Annualized strength decline was ~ 1%. Steeper decline (>1.5%/yr) was associated with old age, greater weight loss, and chronic conditions.	Grip strength only 27 yr follow-up period Japanese-American men
Frontera WR, 2000 [57]	65.4 ± 4.2	M	12	Loss of 24% of initial knee extensor strength (a rate of decline: -1.98 ± 1.22 % / yr) Muscle strength at baseline and the changes in muscle CSA were independent predictors of strength levels at Yr 12. Histology showed a reduction of type I fibers and decreased capillary density.	Only men, 12 yr longitudinal study * Larger reductions of strength in lower extremities compared with the upper extremities
Hughes VA, 2001 [58]	46 - 78 yrs	M F	52 78	The rate of decline in knee extensor strength: 1.4 %/yr The change in leg strength was directly related to the change in muscle mass in both men and women.	9.7 yrs follow up, * longitudinal rates of decline was ~ 60% greater than estimates from a cross-sectional analysis in the same population.

Age-related loss of skeletal muscle mass and strength (sarcopenia) contribute to the development of functional limitations and disability in older adults. Many studies have been showing the relationship of muscle mass and physical limitations and/or muscle strength and disability. [8-9, 11-14] Although both muscle mass and muscle strength are related to physical limitations, muscle strength is more powerful predictor of incident physical limitations. [14] Skeletal muscle weakness has been consistently reported as an independent risk factor for high mortality in older adults. [17-21] Again, low skeletal muscle strength, but not muscle mass, is associated with high mortality in community-dwelling older adults enrolled in the Health ABC Study. [22] As a matter of facts, muscle mass and muscle strength are closely inter-correlated. It has been thought that muscle strength is mainly determined by the quantity of muscle mass because muscle strength is highly correlated with muscle mass (r=0.5~0.7). [5-7] However, muscle strength seems to be influenced by the changes in muscle quality as well. For instance, changes in muscle composition such as reduction of the proportion in type IIb fibers with increase in type I fibers, [59] infiltration of fat cells, [60] and increase in connective tissue components seem to have an important role in relation to functional limitations and disability. Neurological mechanisms like a reduction in alpha motor unit number, slowing of axonal conduction velocity, segmental demyelination also contribute declines in skeletal muscle strength. [61] More recently, it is suggested that alterations in the endocrine milieu and increase in proinflammatory cytokines have important roles in the process of sarcopenia. [62-64]

1.2.3 Diabetes mellitus and skeletal muscle strength (Systematic review)

There are only a few studies examining skeletal muscle strength in diabetes. The previous literature in this topic is reviewed systematically because the association of diabetes and muscle strength is the main topic of the current study.

1.2.3.1 Methods for finding literatures

OVID was used to perform a literature search on the database MEDLINE (1966-2005). The initial search by using key words “muscle strength” and “diabetes” revealed 79 articles. The search was limited to human studies, published in the English language, and with an available electronic abstract. There were 71 articles which remained after this restriction. The abstracts of 71 articles were reviewed to select relevant articles. The following papers were excluded: animal studies, laboratory experimental studies, or review papers. The articles had to meet the following criteria to be included: 1) human subject research, 2) the data had to contain quantitative measurements of skeletal muscle strength. After reviewing 71 abstracts, four studies met all the selection criteria and were included in this review. Two of them studied skeletal muscle strength in type 1 diabetes [65, 66] and the other two studied muscle strength in type 2 diabetes [67, 68]. To summarize, four case control studies were included in this review. Manual screening of the bibliography in the selected article has been performed as well. This literature search was performed on October 15th, 2005.

1.2.3.2 Study design and selection of subjects

In all studies combined, skeletal muscle strength data was available for 144 subjects with diabetes mellitus (100 with type 1 diabetes and 44 with type 2 diabetes) and 152 subjects without diabetes. The study design and characteristics of subjects included in this review are summarized in Table 3. Four studies were case control studies of persons with either type 1 or type 2 diabetes and healthy control subjects. [65-68] In the case control studies, the cases were selected from outpatient clinics of participating hospitals. Particularly, subjects with type 1 diabetes were chosen from those who had duration of diabetes greater than 20 years. For subjects with type 2 diabetes, the mean duration of diabetes was about 9 to 11 years. All four case control studies enrolled only persons with known and treated diabetes in a hospital setting from a single center. In two of the case control studies, the control subjects were recruited among hospital employees, blood donors, friends and relatives, which may contain selection bias. One study did not report the recruitment method and one study recruited the control subjects by advertising in the local press. The control subjects were matched for age, sex, height and weight [65-66, 68] or at least by weight. [67] The study by Halvitsiotis, et al. had no information about the gender of subjects and included lean control subjects with totally different body size (BMI: 25.0 ± 0.5 compared to 29.7 ± 0.9 in type 2 diabetic subjects, p=0.001). [67]

Table 3. Study design and characteristics of subjects included in the studies of skeletal muscle strength in diabetes mellitus, 1996-2005.

Author, publication yr, reference	Study design	Type of diabetes	Cases	Controls
Andersen H. et al., 1996 [65]	Case Control	Type 1	56 cases: 19 women and 39 men Selected from outpatient clinic Diabetes duration > 20 yrs No severe cardiac or lung disease Aged 31 - 64 yrs	56 healthy controls matched for age, sex, height, and weight Recruited among hospital employees, blood donors, friends, and relatives
Andersen H, 1998 [66]	Case Control	Type 1	44 cases: 16 women and 28 men Selected from outpatient clinic Diabetes duration > 20 yrs Age: 46 ± 9 yrs	44 healthy controls matched for age, sex, height, weight and weekly physical activity Recruited among hospital employees, blood donors, friends, and relatives
Halvatsiotis P. et al, 2002 [67]	Case Control	Type 2	8 cases No information about sex Mean duration of diabetes: 8.5 yrs (3-19 yrs), Age: 56 ± 2 yrs	8 weight-matched controls Additional 8 lean control subjects No information about recruitment
Andersen H. et al, 2004 [68]	Case Control	Type 2	36 cases: 13 women and 23 men Mean duration of diabetes 11 yrs (5-26 yrs) Aged 44 - 69 yrs	36 healthy controls matched for age, sex, height and weight Recruited by advertising in the local press

1.2.3.3 Assessments of muscle strength

The methods for the quantitative assessments of skeletal muscle strength of the four studies are presented in Table 4. Three out of four studies measured maximal isokinetic strength (peak torque) using isokinetic dynamometer. [65-66, 68] One study measured peak isometric strength. [67]. Three studies used a LidoActive Multi joint II (Loredan Biomedical, West Sacramento, CA) while two studies used a Kin-Com dynamometer (Chattanooga, TN). Two studies measured muscle fatigability by using either endurance index or fatigue rate. [66-67] Three studies examined muscle strength in both upper and lower extremities, while two studies examined only in lower extremities. However, all four studies measured muscle strength at knee extension, which has been considered as the most physiologically important and reliable site for strength measurements. [23]

Table 4. Summary of measurements and results of skeletal muscle strength in diabetes mellitus, 1996-2005.

Author, publication yr, reference	Measurements	Main findings
Andersen H. et al., 1996 [65]	Isokinetic muscle testing: maximal isokinetic strength (peak torque) of the ankle dorsal and plantar flexion, knee extension and flexion, wrist extension and flexion	21% reduction in ankle dorsal and plantar flexor strength, 16% reduction of knee extensor strength 10-11% non-significant reduction of wrist muscle strength. Muscle weakness is related to the presence and severity of neuropathy.
Andersen H, 1998 [66]	Subjects were instructed to perform 30 maximal isokinetic movements. Endurance index was defined by the work of the last five repetitions as a percentage of the work of the first five repetitions.	Patients with type 1 diabetes had reduced strength of all muscle groups by 14-24%, but increased muscular endurance.
Halvatsiotis P. et al, 2002 [67]	Peak voluntary isometric torque of knee extensor was measured at a knee angle of 60^o of flexion. Fatigue rate was calculated from the line of best fit through the data.	Muscle strength was unaffected by diabetes and glycemic status (before and after glycemic control). Type 2 diabetic subjects showed increased tendency for muscle fatigability.
Andersen H. et al, 2004 [68]	Maximal isokinetic strength (peak torque) of extension and flexion at the ankle, knee, elbow, and wrist was assessed by an isokinetic dynamometer.	17 and 14 % reduction of strength of ankle flexors and extensors, 7% (NS: exact p-value not given) and 14% ($p<0.05$) reductions of strength of knee extensors and flexors, Muscle strength was preserved at the elbow and wrist. Muscle weakness is related to the presence and severity of peripheral neuropathy

1.2.3.4 Muscle strength in subjects with diabetes

Subjects with diabetes, whether type 1 or type 2, showed reduced skeletal muscle strength compared with non-diabetic controls in all studies except the study by Halvatsiotis, et al. (Table 4). [65-68] In fact, even in Halvatsiotis' study, [67] peak isokinetic torque of knee extension was lower in subjects with type 2 diabetes compared to weight-matched control subjects (mean ± SE: 67 ± 9 vs 102 ± 18 Nm), but similar to lean control subjects (79 ± 18 Nm). However, there was no statistically significant difference between groups (p=0.345). [67] It is noticed that their study had small sample size (8 cases and 8 weight-matched controls), which seem to be responsible for the insignificant finding due to low power.

Table 5 summarizes maximal isokinetic strength in subjects with either type 1 or type2 diabetes and controls. The studies in type 1 diabetes consistently show that diabetic patients have reduced strength of muscle groups in the lower extremities. [64-65] However, the difference of muscle strength in the upper extremities was not statistically significant. [65] The findings are quite similar in type 2 diabetes. Andersen et al. reported reduced muscle strength in the lower extremities in subjects with type 2 diabetes. [68] Again, there was no difference in muscle strength of the upper extremities. However, among the four studies reviewed, there was no measurement of skeletal muscle mass. No study reported muscle quality after controlling for the differences in muscle mass between subjects with and without diabetes. Two studies examined muscular endurance. [66, 67] Andersen et al. reported increased muscular endurance in subjects with long standing type 1 diabetes. [66] In contrast, Halvatsiotis et al. showed increased tendency for muscle fatigability in subjects with type 2 diabetes. [67]

Table 5. Results of maximal isokinetic strength in diabetic and control subjects, 1996-2005.

Author, study yr, reference	N	Muscles examined	Diabetic subjects (Nm)	Control subjects (Nm)	P value
Andersen H. et al., 1996 [65]	56	Knee extensor	150.8 ± 38.5	178.6 ± 52.8	<0.0001
		Knee flexor	82.4 ± 20.2	99.6 ± 31.0	<0.01
		Ankle dorsal	24.3 ± 6.8	30.7 ± 7.5	<0.0001
		Ankle plantar	87.8 ± 23.2	111.0 ± 28.7	<0.01
		Wrist extensor	8.5 ± 2.4	9.5 ± 3.2	NS†
		Wrist flexor	15.1 ± 3.6	16.8 ± 5.4	NS
Andersen H, 1998 [66]	44	Knee extensor	117.2 ± 33.0	136.1 ± 39.2	<0.02
		Knee flexor	67.3 ± 21.4	80.1 ± 26.1	<0.02
		Ankle extensor	19.4 ± 4.9	22.9 ± 5.1	<0.005
		Ankle flexor	55.6 ± 14.2	73.0 ± 18.1	<0.005
Halvatsiotis P. et al, 2002 [67]	8	Knee extensor	67 ± 9	102 ± 18 (weight matched control) 79 ± 18 (lean control)	0.345*
Andersen H. et al, 2004 [68]**	36	Knee extensor	Reduced by 7 % in diabetics than controls		0.26
		Knee flexor	Reduced by 14 % in diabetics than controls		<0.05
		Ankle extensor	Reduced by 14 % in diabetics than controls		<0.03
		Ankle flexor	Reduced by 17 % in diabetics than controls		<0.02
		Wrist	No difference		NS
		Elbow	No difference		NS

Data are mean ± SD, except Halvatsiotis' (SE). †NS: Not significant (exact p-value not given in the original article)
*ANOVA test between three groups. ** Actual strength data are not available.

1.2.3.5 Factors associated with muscle strength in diabetes

In both type 1 and type 2 diabetes, muscle strength is related to the presence and severity of peripheral neuropathy, but not with retinopathy or nephropathy. [65-66, 68] The correlations between the neuropathy rank-sum score (NRSS) and muscle strength were moderate to high ($r = -0.41 \sim -0.66$, $p < 0.05$). NRSS was defined as a summation of the rank scores of a neuropathy symptom score, a neurological disability score, and rank scores of electrophysiological measures. [68] In Halvatsiotis' study, muscle strength was unaffected by glycemic status before and after strict glycemic control. [67] However this observation was based on a limited number of samples (8 subjects with type 2 diabetes and 8 control subjects).

1.2.3.6 Limitations of Previous Studies

The studies of skeletal muscle function in subjects with either type 1 or type 2 diabetes showed generally lower muscle strength in diabetic subjects. Only one study by Halvatsiotis, et al. failed to demonstrate a statistically significant difference. [67] It should be considered that lean control subjects in their study were totally different compared with subjects with type 2 diabetes in terms of body size (BMI: 25.0 ± 0.5 versus 29.7 ± 0.9, p=0.001). Halvatsiotis, et al. compared diabetic subjects with lean and weight-matched control groups by analysis of variance test. [67] But, they had to compare only weight matched controls with those with type 2 diabetes by independent t-tests because it has been well known that skeletal muscle strength depends largely on the muscle mass which again closely correlates with body size. [51] Comparison of muscle strength between two groups of subjects with different body size may be confounded by differences in muscle mass. Furthermore, the small sample size (n=24 including 8 cases, 8 lean controls and 8 weight-matched controls) of the study might have limited power to detect true differences.

In both type 1 and type 2 diabetes, lower skeletal muscle strength was observed in lower extremities (ankle and knee), but not in upper extremities (wrist and elbow). In fact, relative preservation of upper extremity strength is a common phenomenon observed in many cross-sectional and longitudinal studies of aging adults. [49, 57-58] It is possible that the neuropathic process of diabetes may have an influence predominantly on the lower extremities. It is consistent with the findings of Andersen et al. [65, 68] They showed that muscle strength is related to the presence and severity of peripheral neuropathy in type 1 as well as type 2 diabetes.

It is also well known that diabetic neuropathy predominantly involves the lower extremities. [69-71]

In the previous case-control studies, researchers tried to match controls for age, sex, height and weight or at least by weight. However, it does not mean that the muscle mass of diabetic subjects and controls are the same. It is well known that subjects with type 2 diabetes are more obese not only in terms of general adiposity as evidence by BMI, but also regional adiposity or central obesity. So, it is still possible that body composition may differ between cases and matched controls. Unfortunately, previous studies did not measure body composition with state of the art technology, [72] and therefore could not adjust for the muscle mass. The measure of muscle quality is a more reasonable indicator of contractile function of skeletal muscle than crude muscle strength, which is largely dependent on the quantity of muscle mass. This concept might be important particularly for the comparison of skeletal muscle function between subjects with different body size like those with and without diabetes.

Only a few studies have tried to identify factors associated with muscle strength and quality in diabetes. [65, 68] In both type 1 and type 2 diabetes, muscle strength is associated with the presence and severity of peripheral neuropathy, but not with retinopathy or nephropathy. However, it is hard to generalize the findings because subjects with type 1 diabetes in their study had a long duration of diabetes more than 20 years. [65, 66] Further research is needed to investigate whether this association is present in persons with shorter duration of diabetes as well.

In summary, skeletal muscle strength is lower in subjects with diabetes regardless of type 1 or type 2 diabetes. Lower extremities are predominantly affected by diabetes with relative preservation of upper extremity strength. The major problem with previous studies on skeletal muscle strength and diabetes is limited external validity because they selected severe cases with long duration of diabetes in the hospital setting. Population based cross-sectional and prospective cohort studies are needed to examine the association of diabetes with skeletal muscle strength and to investigate whether subjects with diabetes experience longitudinal declines in muscle strength and muscle quality.

1.3. LITERATURE CITED

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2. ARTICLE ONE: DECREASED MUSCLE STRENGTH AND QUALITY IN OLDER ADULTS WITH TYPE 2 DIABETES: THE HEALTH, AGING AND BODY COMPOSITION STUDY

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by The American Diabetes Association

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2.1 ABSTRACT

Adequate skeletal muscle strength is essential for physical functioning and low muscle strength is a predictor of physical limitations. Older adults with diabetes have a 2- to 3-fold increased risk of physical disability. However, muscle strength has never been investigated with regard to diabetes in a population-based study. We evaluated grip and knee extensor strength and muscle mass in 485 older adults with diabetes and 2,133 without diabetes in the Health, Aging and Body Composition Study. Older adults with diabetes had greater arm and leg muscle mass than those without diabetes as they were bigger in body size. Despite this, muscle strength was lower in men with diabetes and not higher in women with diabetes than corresponding counterparts. Muscle quality, defined as muscle strength per unit regional muscle mass, was significantly lower in men and women with diabetes than those without diabetes in both upper and lower extremities. Furthermore, longer duration of diabetes (≥ 6 yrs) and poor glycemic control (HbA1c > 8.0 %) were associated with even poorer muscle quality. In conclusion, diabetes is associated with lower skeletal muscle strength and quality. These characteristics may contribute to the development of physical disability in older adults with diabetes.

2.2 INTRODUCTION

In the United States, people 65 years and older will make up most of the diabetic population in the next 25 years. Furthermore, the proportion of the diabetic population 75 years or older is projected to exceed 30 % by 2050. [1, 2] In older adults, diabetes has been associated with a 2- to 3- fold increased risk of developing physical disability. [3-6] Moreover, we have reported the association of diabetes with subclinical functional limitation in the Health, Aging and Body Composition (Health ABC) Study. [7] However, the mechanism for impaired physical function in diabetes has been poorly understood. Chronic conditions frequently combined with diabetes such as coronary heart disease, peripheral artery disease, visual impairment, and depression partially explained the association but still 40 % of excess risk for physical disability remained unexplained. [4, 6]

Low muscle strength, but not muscle mass, is associated with poor physical function in older men and women. [8, 9] Muscle strength measured in midlife or old age is highly predictive of functional limitations and disability up to 25 years later. [10-12] However, the effects of diabetes on muscle strength and quality have never been investigated in a population-based study. Because most individuals with diabetes are obese and have bigger muscle mass, as well as increased total body fat mass, direct comparison of their muscle strength with those without diabetes may be misleading. With the advent of body composition analysis, we are now able to precisely measure regional muscle mass and quantitatively assess in vivo skeletal muscle quality defined as maximal voluntary contractile force or torque per unit regional muscle mass of the specific body compartment. [13]

In the present study, we evaluated hand grip and knee extensor strength and muscle quality in community dwelling older adults with and without diabetes in the Health ABC study. To evaluate the cumulative effects of metabolic derangements of diabetes on skeletal muscle function, subjects with diabetes were further categorized by the duration of diabetes and the level of glycemic control.

2.3 METHODS

2.3.1 Participants

The Health ABC Study included 3,075 well functioning older adults, of whom 51.6% were women and 41.6% African-Americans. Whites were recruited from a random sample of Medicare beneficiaries residing in ZIP codes from the metropolitan areas surrounding Pittsburgh, Pennsylvania and Memphis, Tennessee. African-Americans were recruited from all age-eligibles in these geographic areas. Eligibility criteria included: aged 70 to 79 in the recruitment period from March 1997 to July 1998; self-report of no difficulty walking one-quarter of a mile or climbing 10 steps without resting; no difficulty performing basic activities of daily living; no reported use of a cane, walker, crutches or other special equipment to ambulate; no history of active treatment for cancer in the prior 3 years; and no plan to move out of the area in the next 3 years. All individuals gave informed consent for participation in the study and the consent forms and study protocols were approved by the institutional review boards at each field center. Among 3,075 participants, 29 (0.9%) who had missing fasting plasma glucose concentrations were excluded and 6 subjects with the onset of diabetes before age 25 were considered as having type

1 diabetes and excluded from the analyses. Among the remaining 3,040 participants, 389 subjects (12.8 %) were excluded from the knee strength test due to uncontrolled hypertension, history of stroke or aneurysm in the brain, bilateral knee joint replacement, presence of severe bilateral knee pain, or refused by the participant. Another 33 (1.1%) who had missed body composition assessment by dual energy X-ray absorptiometry (DXA) were also excluded. Finally, 2,618 participants (85.1 % of original cohort), including 485 (18.5 %) with type 2 diabetes and 2,133 without diabetes, who had completed muscle strength test and DXA measurements of body composition, were included in the analyses.

2.3.2 Assessment of diabetes

Participants were considered as having type 2 diabetes if they had either (i) a report of having been diagnosed as diabetes with the onset after age 25 and/or (ii) current use of oral hypoglycemic medications or insulin, or (iii) having a fasting plasma glucose concentration equal or greater than 7.0 mmol/l. [14] We used information on reported age at diagnosis to define diabetes duration; for participants with newly diagnosed diabetes, the duration of diabetes were considered as zero. The duration of diabetes ranged from 0 to 45 years with the median of 6.0 years. Plasma glucose was measured using an automated glucose oxidase reaction (Vitros 950 analyzer, Johnson and Johnson, Rochester, NY) and a glycosylated hemoglobin (HbA_{1c}) was measured in all participants by enzymatic method (Bio-Rad, Hercules, CA).

2.3.3 Assessment of body composition

Body weight and height were measured in a hospital gown and without shoes on a calibrated balance beam scale and stadiometer, respectively, and a body mass index (BMI) in kg/m^2 was calculated. Lean mass of the upper and lower extremities as well as the total body were assessed using DXA (Hologic QDR 4500, software version 8.21). Bone mineral content was subtracted from the total and regional lean mass to define total non-bone lean mass, which represents primarily skeletal muscle in the extremities. [15] Total body fat mass was measured and percent body fat was calculated.

2.3.4 Assessment of muscle strength

Muscle strength was measured using an isokinetic dynamometer (Kin-Com dynamometer, 125 AP, Chattanooga, TN) for knee extension and isometric dynamometer (Jaymar, JLW Instruments, Chicago, IL) for grip strength. For knee extension, maximal voluntary concentric isokinetic torque was assessed in Newton-meters (Nm) at angular velocity of 60^{o}/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. Isometric grip strength was assessed for each hand. Participants with severe hand pain or recent surgery were excluded. The vast majority (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; Nm/kg, arm specific force; kg/kg) was created by taking the ratio of strength to the entire corresponding leg or arm muscle mass in kg measured by DXA. [13]

2.3.5 Other covariates

Sociodemographic characteristics included age, gender, race, and education. Combined chronic health conditions were summarized as comorbidity score which was defined as number of the following ten prevalent conditions: coronary heart disease, congestive heart failure, cerebrovascular disease, peripheral artery disease, knee osteoarthritis, hypertension, depression, pulmonary disease, cancer, and osteoporosis. Each condition was 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 greater than 1.5 mg/dl in men, and 1.2 mg/dl in women. [16] Health-related behaviors which included current smoking, alcohol drinking, and physical activity, were also considered as potential confounders. Level of total physical activity (kcal/week) was determined using a standardized questionnaire designed specifically for the Health ABC Study. [17]

2.3.6 Statistical analysis

Differences in means and proportions of baseline characteristics and body composition by diabetes status were tested using Student's t-tests and chi-square tests. Differences in muscle strength and quality between subjects with and without diabetes were also assessed by independent t-tests. There was a significant interaction between diabetes status and gender in relation to muscle strength ($p = 0.003$). Therefore, all of the following analyses were stratified by gender. Adjustments for potential confounders were performed using multiple regression models by cumulative addition of sociodemographic factors and physical activity (model 1), plus body mass index (model 2), plus smoking, alcohol drinking, combined chronic health conditions, and diabetes related complications (model 3). To test the effects of duration and severity of diabetes on muscle strength and quality, analysis of variance (ANOVA) tests for trend were used. When overall differences were significant with ANOVA, post hoc comparisons were performed with Bonferroni adjustment. A p-value of <0.05 was accepted as statistically significant. All the analyses were performed using SPSS software (version 12.0.0, SPSS Inc., Chicago, IL).

2.4 RESULTS

Among 485 older adults with type 2 diabetes, 389 (80.2%) had previously known diabetes while 96 (19.8%) were newly diagnosed by fasting plasma glucose criteria. Most diabetic subjects were treated with oral hypoglycemic medications (216, 44.5%) or insulin injections (99, 20.4%), while one third (170, 33.7%), including newly diagnosed subjects, were taking no diabetic medications. Participants with diabetes were more likely to be black, and less educated. Older men and women with diabetes had higher weight, BMI, total body fat, and total body lean mass than nondiabetic counterparts. As expected, diabetes-related complications, such as impaired vision and renal insufficiency were twice more prevalent in those with diabetes. Older adults with diabetes also had higher comorbidity scores compared to nondiabetic subjects. Those with diabetes reported less alcohol use and less physical activity (Table 6).

Table 7 presents arm and leg muscle strength, corresponding regional muscle mass, and muscle quality by diabetes status. In men, those with diabetes showed significantly lower muscle strength in both upper and lower extremity ($p < 0.05$, each) although their arm and leg regional muscle mass were significantly greater than those without diabetes ($p < 0.001$, each). In women, absolute arm and leg muscle strength were not significantly different in those with diabetes in spite of greater arm and leg regional muscle mass than those without diabetes. Muscle quality was consistently lower in both upper and lower extremities in both men and women with diabetes compared to nondiabetic counterparts (all; $p < 0.001$, Table 7). There was no significant difference in the relationship of diabetes to muscle quality in blacks compared to whites (p for interaction = 0.31 and 0.70 in men, 0.17 and 0.76 in women for leg and arm muscle quality respectively).

Lower muscle quality in men and women with diabetes was slightly attenuated after adjustment for race, age, clinic site, and physical activity (Table 8, model 1). However, adjustment for BMI attenuated the difference in muscle quality by 17 to 37 % in men and by 49 to 69 % in women (Table 8, model 2). Adjustment for total fat mass instead of body mass index gave the same result (data not shown). Further adjustments for smoking, alcohol drinking, combined chronic diseases, impaired vision, and renal insufficiency virtually eliminate the effect of diabetes on muscle quality in women. But, in men, lower muscle quality associated with diabetes remained even in the fully adjusted model (Table 8, model 3).

Muscle quality was associated with diabetes duration in both upper and lower extremities in both men and women. Those with the longer duration of diabetes (≥ 6 years) showed the lowest muscle quality (Figure 1). There was also a linear trend between the level of glycemic control and muscle quality. Diabetic subjects with poor glycemic control (HbA1c > 8.0 %) had the lowest muscle quality regardless of sex and muscle groups examined (Figure 2).

2.5 DISCUSSION

In our study, older adults with type 2 diabetes had a greater muscle mass in their arm and leg than those without diabetes. But despite this larger muscle mass, those with diabetes were either weaker (men) or not stronger (women) than those without diabetes. This finding was somewhat surprising because the quantity of muscle mass had been known as a primary determinant of muscle strength. [13, 18-20] We have clearly demonstrated that muscle quality was consistently lower in older adults with type 2 diabetes, regardless of sex and muscle groups examined (arm or leg). This is a novel finding possibly explaining a pathophysiological mechanism for increased risk of functional limitations and disability in older adults with type 2 diabetes, because low muscle strength or poor muscular function is predictive of physical disability. [8-12] Our finding is consistent with the study in patients with type 1 diabetes. [21] We have also found that lower muscle quality in older adults with diabetes was largely attenuated by adjustment for BMI, indicating obesity might have important role in this association. We have previously reported that skeletal muscle attenuation coefficient determined by computerized tomography was lower with increasing BMI and it was independently associated with muscle strength and quality. [22] Low muscle attenuation was also found in older adults with impaired glucose tolerance or type 2 diabetes. [23] Reduced muscle attenuation values have been associated with reduced oxidative enzyme activity [24] and lower maximal aerobic capacity. [25] It is possible that alterations of muscle composition with increased fat infiltration into the skeletal muscle as evidenced by low muscle attenuation in type 2 diabetes, which is also associated with combined obesity, may result in poor muscle quality. Further research will be needed to determine whether diabetes itself or the higher levels of body fat in the diabetes is a direct cause of poor muscle quality in a prospective study.

There had been no report on skeletal muscle strength or function in type 2 diabetes until Andersen et al. reported muscle weakness at the ankle and knee in a case-control study. [26] They showed a 7 to 17 % lower muscle strength at the ankle and knee in patients with type 2 diabetes compared to controls. Although control subjects were matched for sex, age, weight, height, and physical activity, it was impossible to evaluate whether muscle weakness in subjects with type 2 diabetes was due to reduced muscle mass or poor muscle quality because muscle mass was not assessed in their study. In the present study, we measured arm and leg regional muscle mass separately by DXA. The concurrent measures of muscle mass and strength allowed us to evaluate in vivo muscle quality, which was defined as muscle strength per unit muscle mass in kg. This definition has been consistently used to assess muscle function in human subjects. [13, 27-28] The specific force of arm and specific torque of leg represent the maximal contractile capacity of each appendicular skeletal muscle group adjusted for the quantity of muscle mass. Therefore, these measures of muscle quality are more reasonable indicator of contractile function of skeletal muscle than crude muscle strength, which is largely dependent on the quantity of muscle mass. This concept might be important particularly for the comparison of skeletal muscle function between subjects with different body size like those with and without diabetes.

The discrepancy between men and women in terms of differences in absolute muscle strength can be explained by the magnitude of differences in muscle mass between those with and without diabetes. Older men with diabetes had only slightly (4~5 %) higher appendicular muscle mass than those without diabetes (Table 7). This small difference in muscle mass may not be enough to overcome poor muscle quality of diabetes, resulting in lower muscle strength in men with diabetes. But, women with diabetes had moderately (12~14 %) higher appendicular muscle mass than those without diabetes, which may be enough to compensate poor muscle quality and result in absolute muscle strength comparable to the non-diabetic women. However, despite of having similar muscle strength, older women with diabetes showed poor physical function in our previous report using the same cohort [7], suggesting their strength might be insufficient to carry their heavy weight.

Another important finding of this study is a linear relationship showing both longer duration of diabetes and poor glycemic control are associated with much poorer muscle quality (Figure 1 and 2). These findings are consistent with our previous observation that poor glycemic control in diabetic individuals explained the association with subclinical functional limitation. [7] A metabolic consequence of uncontrolled hyperglycemia is catabolism which, depending on the severity, is accompanied by muscle protein breakdown and inadequate energy utilization, potentially resulting in poor muscle function. Diabetes with poor glycemic control is also associated with increased systemic inflammatory cytokines, such as TNF-α and IL-6, which have detrimental effects on muscle function. [29-32]

Neuropathic processes involving motor neurons might be another possible underlying mechanism for the poor muscle function in diabetes. In the mouse model, after 4 weeks of diabetes, the relative loss of torque via nerve stimulation (~43 %) was greater than the force loss in the directly stimulated muscle (~24 %), indicating a functional neural deficit. [33] Although it is unclear in humans, a greater and selective atrophy of type IIb fibers have been observed in diabetic animal muscles [34-36], which may contribute to strength loss. In humans, the presence and severity of diabetic neuropathy has been shown to be associated with decreased muscle strength in both type 1 and type 2 diabetes. [26, 37] Electrophysiologic studies suggest that loss of muscle strength in diabetic patients is due to incomplete reinnervation following axonal loss. [38]

The present study is the first epidemiologic study to assess skeletal muscle function in subjects with and without type 2 diabetes in apparently healthy, community dwelling older adults. The population includes white and black older men and women with type 2 diabetes in various clinical stages. We found a significantly lower muscle quality in older adults with diabetes though the difference is relatively small in magnitude. For the clinical implications, we have to consider that subjects with diabetes in this study were all well functioning without physical disability. The inclusion of asymptomatic subjects as diabetes group by fasting plasma glucose cut-point attenuated the difference in muscle quality (data not shown). In other words, older adults with diabetes seen in clinical setting might have even poorer muscle quality. It has been well established that lower muscle strength is an important contributor to disability. [10-12] However, the clinical significance of poor muscle function in diabetes for the development of disability can only be answered by a prospective study.

This study has several limitations. First of all, this is a cross-sectional study showing only an association between type 2 diabetes and poor muscle function. It does not necessarily mean that type 2 diabetes in older adults result in poor muscle strength and quality. It is also possible that lower muscle quality is a causative factor related to the development of type 2 diabetes in older adults. However, even lower muscle quality in diabetic subjects with longer duration and poor glycemic control may suggest that poor muscle quality is likely a consequence rather than a cause of diabetes in older adults (Figure 1 and 2). Second, we have no data on diabetic neuropathy at baseline, which may have important mediating role in muscle weakness. Despite these limitations, this study might have important public health implications as older adults with diabetes are at increased risk of developing physical disability and potential preventive strategies are available including resistive-training exercise program to improve skeletal muscle function in subjects with diabetes. [39]

In conclusion, type 2 diabetes is associated with lower skeletal muscle strength and quality in community dwelling older adults. These characteristics may contribute to development of physical disability in older adults with diabetes. Prospective studies are needed to investigate whether type 2 diabetes in older adults is associated with longitudinal declines in muscle strength and examine the relationship to the loss of muscle mass and muscle quality.

Table 6. Characteristics of the study population by diabetes status, according to gender

	Men			Women		
	No diabetes (n, 1,004)	Diabetes (n, 273)	*p*	No diabetes (n, 1,129)	Diabetes (n, 212)	*P*
Age (years)	73.7 ± 2.9	73.8 ± 2.9	0.47	73.5 ± 2.8	73.2 ± 2.8	0.19
Black (%)	32.2	45.4	<0.01	40.3	68.9	<0.01
Education < 12 yrs (%)	24.5	32.0	0.01	19.8	37.1	<0.01
Height (cm)	173.3 ± 6.5	173.5 ± 6.1	0.63	159.6 ± 6.2	159.6 ± 5.6	0.93
Weight (kg)	80.3 ± 12.6	85.3 ± 13.8	<0.01	69.2 ± 14.1	76.9 ± 14.1	<0.01
BMI (kg/m^2)	26.7 ± 3.8	28.3 ± 4.0	<0.01	27.1 ± 5.2	30.2 ± 5.4	<0.01
Total body fat (kg)	22.8 ± 6.9	24.9 ± 7.4	<0.01	27.9 ± 9.0	31.5 ± 9.2	<0.01
Total body lean (kg)	54.9 ± 7.0	57.5 ± 7.4	<0.01	39.5 ± 5.8	43.4± 5.8	<0.01
Fasting glucose (mmol/l)	5.3 ± 0.5	8.5 ± 2.9	<0.01	5.1 ± 0.5	8.4 ± 3.1	<0.01
HbA_{1C} (%)	6.0 ± 0.5	7.8 ± 1.5	<0.01	6.0 ± 0.5	8.0 ± 1.6	<0.01
Impaired vision (%)	18.7	28.3	<0.01	17.6	27.5	<0.01
Renal insufficiency (%)	7.5	15.9	<0.01	8.0	14.4	<0.01
Comorbidity score *	1.25 ± 1.12	1.55 ± 1.18	<0.01	1.38 ± 1.14	1.78 ± 1.27	<0.01
Smoking (current, %)	10.7	9.5	0.59	9.5	9.9	0.85
Alcohol drinking (%)	60.6	46.2	<0.01	47.4	22.6	<0.01
Physical activity (kcal/week)	5,397	4,761	0.07	4,808	4,092	<0.01

Data are means ± SD or proportion (%), except physical activity (median).
*Comorbidity score: number of combined chronic diseases including coronary heart disease, congestive heart failure, cerebrovascular disease, peripheral artery disease, knee osteoarthritis, hypertension, depression, pulmonary disease, cancer, and osteoporosis.

Table 7. Comparison of arm and leg muscle strength, regional muscle mass, and muscle quality by diabetes status, stratified by gender

	Men			Women		
	No diabetes (n, 1,004)	Diabetes (n, 273)	*p*	No diabetes (n, 1,129)	Diabetes (n, 212)	*p*
Leg strength (Nm)	133.0 ± 32.4	128.5 ± 34.6	0.046	81.1 ± 22.0	83.8 ± 21.4	0.096
Leg muscle mass (kg)	8.7 ± 1.3	9.1 ± 1.4	<0.001	6.3 ± 1.2	7.0 ± 1.2	<0.001
Leg muscle quality (Nm/kg)	15.3 ± 3.2	14.2 ± 3.3	<0.001	13.0 ± 3.1	12.1 ± 3.2	<0.001
Hand grip strength (kg)	40.0 ± 8.9	38.7 ± 8.8	0.037	24.3 ± 6.4	25.1 ± 5.9	0.098
Arm muscle mass (kg)	3.4 ± 0.6	3.6 ± 0.6	<0.001	2.1 ± 0.4	2.3 ± 0.4	<0.001
Arm muscle quality (kg/kg)	11.7 ± 2.4	10.8 ± 2.3	<0.001	12.0 ± 2.9	11.0 ± 2.9	<0.001

Data are means ± SD.

Table 8. Multiple regression models showing the effect of diabetes on arm and leg muscle quality, stratified by gender

	Men			Women		
	β for diabetes	S.E.	*p*	β for diabetes	S.E.	*p*
Arm muscle quality (kg/kg)						
Unadjusted	-0.89	0.16	<0.001	-1.05	0.22	<0.001
Model 1	-0.84	0.16	<0.001	-0.85	0.22	<0.001
Model 2	-0.53	0.16	0.001	-0.43	0.21	0.043
Model 3	-0.50	0.16	0.002	-0.34	0.22	0.111
Leg muscle quality (Nm/kg)						
Unadjusted	-1.10	0.22	<0.001	-0.87	0.24	<0.001
Model 1	-1.01	0.22	<0.001	-0.61	0.24	0.011
Model 2	-0.84	0.22	<0.001	-0.19	0.23	0.404
Model 3	-0.80	0.22	<0.001	-0.15	0.24	0.524

Adjustments of covariates were performed using multiple regression analyses by cumulatively adding the following covariates into the model
Model 1: race, age, clinic site, and physical activity
Model 2: model 1 + body mass index
Model 3: model 2 + smoking, drinking, comorbidity score, impaired vision, and renal insufficiency

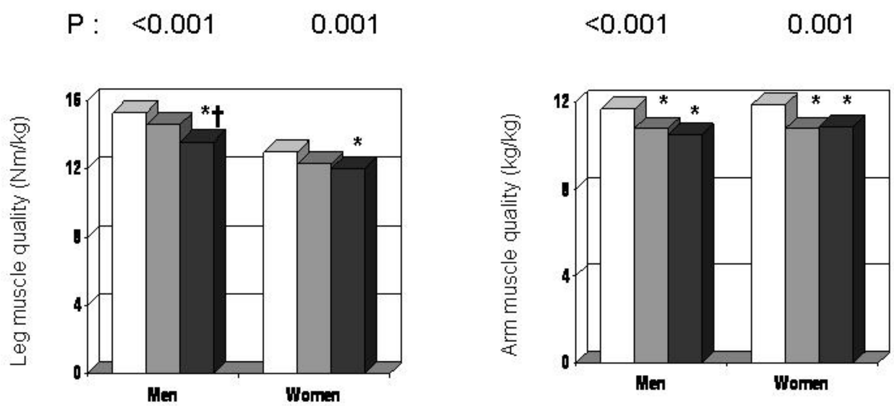

Figure 1. Muscle Quality in subjects without diabetes (□), diabetic subjects with duration < 6 yrs (■), and with duration ≥ 6 yrs (■).
P: p values for linearity, * p < 0.05 compared to subjects without diabetes,
† p < 0.05 compared to diabetic subjects with duration < 6 yrs.

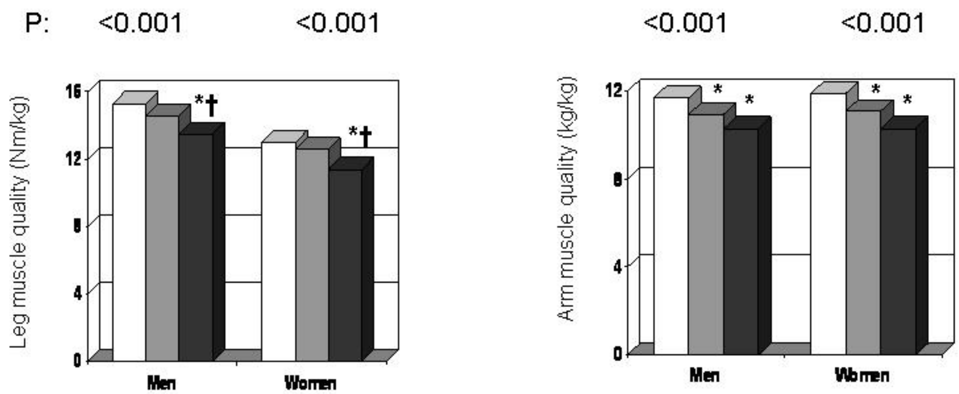

Figure 2. Muscle Quality in subjects without diabetes (□), diabetic subjects with HbA1C ≤ 8.0 % (▪), and with HbA1C > 8.0 % (■).
P: p values for linearity, * p < 0.05 compared to subjects without diabetes,
† p < 0.05 compared diabetic subjects with HbA1c ≤ 8.0 %.

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3. ARTICLE TWO: ACCERELATED LOSS OF SKELETAL MUSCLE STRENGTH IN OLDER ADULTS WITH TYPE 2 DIABETES: THE HEALTH, AGING AND BODY COMPOSITION STUDY

3.1 ABSTRACT

Maintenance of skeletal muscle strength is essential for physical functioning and decreased muscle strength is a predictor of mobility limitations. Older adults with diabetes have a two- to threefold increased risk of physical disability. It is also reported that diabetes in older adults is associated with low muscle strength. However, it is unknown whether low muscle strength is a precedence or consequence of diabetes because longitudinal change of muscle function in diabetes has yet to be investigated. We examined leg and arm muscle mass and strength at baseline and 3 years later in 1,840 older adults in the Health, Aging and Body Composition Study. Both diabetic and non-diabetic older adults lost significant amount of muscle mass and strength in three years. Older adults with type 2 diabetes showed about 50% more rapid decline in the leg muscle strength compared with older adults without diabetes ($p=0.001$). Leg muscle quality, expressed as a maximal strength per unit muscle mass (Nm/kg), also declined more rapidly in older adults with type 2 diabetes ($p<0.05$). 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, combined chronic diseases, and inflammatory cytokines. In conclusion, older adults with type 2 diabetes showed accelerated loss of lower extremity muscle strength, which may be responsible for increased risk of mobility limitations.

3.2 INTRODUCTION

In industrialized countries, the major increase in the number of people with diabetes is attributed to the aging of the population. [1-2] The current burden of diabetes is already greatest in the population ≥ 65 years of age in the United States. Furthermore, the greatest increases in prevalence are expected among the elderly and eventually older adults ≥ 65 years old will make up 70 % of diabetic population in the next 25 years. [2] In older adults, diabetes is associated with a two- to threefold increased risk of developing physical disability. [3-7] Several factors have been identified as contributors to diabetes-related disability including obesity [3-4], coronary heart disease [3-4, 6], stroke [3], arthritis [3-4], depression [6], and visual impairments [3-4]. But still a large portion of diabetes-physical disability relationship is not explained by above factors. Alterations in muscular function in diabetes can be a potential pathway not yet fully explored.

Muscle weakness in diabetes has been considered as a rare manifestation associated with severe diabetic neuropathy. However, recent studies using quantitative assessments of muscular function showed that skeletal muscle strength, especially in lower extremity, is lower in adults with diabetes than non-diabetic controls. [8-10] In the Health ABC Study, we have shown that older adults with type 2 diabetes have lower skeletal muscle strength and quality, defined as a maximal strength per unit muscle mass. [10] But, the previous studies have limitations of cross-sectional observation and it is unclear whether low muscle strength in diabetes is a consequence of diabetes or just a coincidence.

In the present study, we reexamined knee extensor and hand grip strength and body composition three years after baseline examination in the Health ABC Study to investigate longitudinal changes in skeletal muscle strength and quality in relation to baseline diabetes status. We hypothesized that older adults with type 2 diabetes would show a greater declines in skeletal muscle function than older adults without diabetes.

3.3 METHODS

3.3.1 Participants

The Health ABC Study included well-functioning community-dwelling older adults aged 70 to 79 years, of whom 51.6% were women and 41.6% were black. Whites were recruited from a random sample of Medicare beneficiaries residing in ZIP codes from the metropolitan areas surrounding Pittsburgh, Pennsylvania and Memphis, Tennessee. Blacks were recruited from all age-eligible residents in these geographic areas. Eligibility criteria included: age 70 to 79 years old in the recruitment period from March 1997 to July 1998; self-report of no difficulty walking one-quarter of a mile or climbing 10 steps without resting; no difficulty performing basic activities of daily living; no reported use of a cane, walker, crutches or other special equipment to ambulate; no history of active treatment for cancer in the prior 3 years; and no plan to move out of the area in the next 3 years.

Of the 3,075 participants, we excluded those with missing data on fasting plasma glucose (n = 29), those with diabetes onset before age 25 (n = 6), and those who had missing data on body composition (n =33). We also excluded 389 subjects (12.8%) from the knee strength test due to uncontrolled hypertension, history of stroke or aneurysm in the brain, bilateral knee joint replacement, presence of severe bilateral knee pain, or refusal by the participant. Of the 2,618 participants with complete baseline data, 1,840 (70.3 %) were reexamined for skeletal muscle strength and body composition at three years after baseline assessment. The reasons for not having 3-year follow-up data were death (n = 146), no clinic visit due to disability and/or institutionalization (n = 302; home examination, 245; proxy interview, 57), missed contact (n = 77), withdrawal of the participants (n =11), unable to perform 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.

3.3.2 Assessment of diabetes

Participants were considered as having type 2 diabetes if they had either (i) a report of having been diagnosed as diabetes with the onset after age 25 and/or (ii) current use of oral hypoglycemic medications or insulin, or (iii) having a fasting plasma glucose concentration equal or greater than 7.0 mmol/l at baseline. We used information on reported age at diagnosis to define diabetes duration; for participants with newly diagnosed diabetes, the duration of diabetes were considered as 0. The duration of diabetes was ranged 0 to 45 years from time of diagnosis. The average duration was 9.7 ±10.9 years with the median of 5 years. Plasma glucose was measured using an automated glucose oxidase reaction (Vitros 950 analyzer, Johnson and Johnson, Rochester, NY) and a glycosylated hemoglobin (HbA_{1c}) was measured by enzymatic method (Bio-Rad, Hercules, CA).

3.3.3 Assessment of body composition

Body weight and height were measured in a hospital gown and without shoes on a calibrated balance beam scale and stadiometer, respectively, and a body mass index (BMI) in kg/m^2 was calculated. Lean mass of the upper and lower extremities as well as the total body were assessed using dual energy x-ray absorptiometry (DXA, Hologic QDR 4500, software version 8.21). Bone mineral content was subtracted from the total and regional lean mass to define total non-bone lean mass, which represents primarily skeletal muscle in the extremities. Total body fat mass was also measured and percent body fat was calculated.

3.3.4 Assessment of muscle strength

Strength was measured using an isokinetic dynamometer (Kin-Com dynamometer, 125 AP, Chattanooga, TN) for knee extension and isometric dynamometer (Jaymar, JLW Instruments, Chicago, IL) for grip strength. For knee extension, maximal voluntary concentric isokinetic torque was assessed in Newton-meters (Nm) at angular velocity of 60^o/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 the validation of knee strength assessments, we performed a reliability study in 63 participants. The inter-examiner coefficient of variation (CV) was 4.85 % with no significant differences between examiners. The intra-participant 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 (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; Nm/kg, arm specific force; kg/kg) was created by taking the ratio of strength to the entire corresponding leg or arm muscle mass in kg measured by DXA. Changes in muscle strength and quality were calculated as year 3 value minus baseline value, hence negative value means loss of muscle strength or quality.

3.3.5 Other covariates

Sociodemographic characteristics included age, gender, 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 greater than 1.5 mg/dl in men, and 1.2 mg/dl in women. [10] Ankle-arm index (AAI) was calculated and subclinical peripheral artery disease was defined by AAI < 0.9. Health-related behaviors included current smoking, alcohol drinking, and level of total physical activity (kcal/week) determined by using a standardized questionnaire designed specifically for the Health ABC Study. [11]

3.3.6 Statistical analysis

Baseline characteristics of the cohort are presented separately for those with and without diabetes. Chi-square tests were calculated for categorical variables and a *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 (year 4 value minus initial value) and relative terms (percent change from baseline). Differences between participants with and without diabetes were assessed by general linear models controlling for sex, race, age, clinic site, and baseline values when using absolute changes (model 1). Additional adjustments were made for body mass index, baseline muscle mass, and changes in muscle mass or weight change in case of muscle quality because it is already adjusted for muscle mass (model 2), plus combined chronic diseases, and diabetes related complications (model 3), and health related behaviors such as smoking, alcohol drinking, and physical activity (model 4). There was no indication of interaction effect ($p<0.10$) of sex or race with diabetes on the changes in muscle strength or muscle quality. A p-value of <0.05 was accepted as statistically significant. All the analyses were performed using SPSS software (version 12.0.0, SPSS Inc., Chicago, IL).

3.4 RESULTS

Among the 1,840 participants with complete assessments of baseline and year 3 follow-up strength test and body composition, 305 (16.6%) had type 2 diabetes at baseline. Older adults with type 2 diabetes were more likely to be men, black and have a lower level of education (Table 9). Those with diabetes had greater body weight, body mass index, total fat mass as well as higher total lean mass than non-diabetic 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. Interleukin-6 and tumor necrosis factor-α levels were significantly higher in older adults with diabetes (Table 9).

Both diabetic and non-diabetic older adults lost significant amount of initial muscle strength in three years. However, older adults with type 2 diabetes lost their knee extensor strength more rapidly than those without diabetes ($p=0.001$, Table 10). Older adults with type 2 diabetes also lost greater amount of leg lean mass than those without diabetes ($p<0.05$). Furthermore, muscle quality (maximal strength per unit muscle mass, Nm/kg) 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 about 50 % more rapid loss of knee extensor strength (-9.0 % vs. -13.5 %, $p=0.002$) and muscle quality (-6.2 % vs. -10.0 %, $p=0.01$) than those without diabetes (Figure 3). 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 amount of arm muscle mass (Table 10, Figure 3).

Table 11 presents the changes in knee extensor strength and muscle quality controlling for potential confounders. A greater decline of knee extensor strength in participants with type 2 diabetes was not changed by adjustments for sex, race, age, clinic site, body mass index, baseline strength, and changes in leg muscle mass (model 2). This association of diabetes and loss of knee extensor strength was slightly attenuated by additional adjustments for combined chronic diseases and inflammatory cytokines (Table 11, model 3 and 4).

A greater decline of leg muscle quality in older adults with type 2 diabetes were evident after adjustments for demographics, body mass index, baseline muscle quality, and changes in leg lean mass (p=0.001, model 2). Further adjustments for combined chronic diseases and inflammatory cytokines attenuated only minimally the association of diabetes and declines of muscle quality. The greater declines of muscle strength and quality in older adults with type 2 diabetes were remained significant throughout the models (Table 11). Further adjustments for smoking, alcohol drinking, and level of physical activity did not change the results (data not shown).

3.5 DISCUSSION

In this study, older adults with type 2 diabetes lost 13.5 % of their knee extensor strength while those without diabetes lost 9.0 % of initial strength in three years. About 50 % more rapid decline in the knee extensor strength in older adults with diabetes was not accounted 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. [13-16] 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 yet to be well identified. This is the first study showing that type 2 diabetes is associated with rapid loss of skeletal muscle mass and strength in older adults. It confirms previous cross sectional findings of lower muscle strength in individuals with diabetes. [8-10] The finding of this longitudinal study strongly suggest that low muscle strength in adults with type 2 diabetes is a consequence rather than just a coincidence of type 2 diabetes.

We found discordance between upper and lower extremities regarding diabetes and changes in muscle strength over time. In general, a relative preservation of upper extremity strength has been observed in the process of aging. [16-17] 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. [8] Andersen et al. reported that upper extremity strength was preserved even in long-standing type 1 diabetic patients with greater than 20 years of duration. [9] 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. [8-9] It is well known that lower extremities are predominantly involved in diabetic neuropathy presumably due to a length-dependent degeneration of nerve fibers. [18-19] Therefore, skeletal muscle function is more likely to be affected by diabetes in the lower extremities than in the upper extremities. In our study, overall decline in hand grip strength was less than 1 % per year while knee extensor strength declined more than 3 % per year (Figure 3). It is possible that the small changes in hand grip strength make it even more difficult to detect any real differences associated with diabetes. The exclusion of many participants for year 3 knee extensor strength test may also biased the results to the null because proportionally more subjects with diabetes were excluded due to high mortality and other reasons (Table 12). We identified 47 participants with diabetes and 181 without diabetes who were excluded from knee strength test due to contraindications but had hand grip strength data at year 3. Among them, declines in hand grip strength were greater in older adults with diabetes than those without diabetes (-3.3 ± 6.7 vs. -1.1 ± 6.2 kg, $p<0.05$, Table 13), suggesting a strict criteria for knee strength testing might select stronger persons and actually obscure the true declines in muscle strength particularly in those with diabetes.

Lower extremity strength is essential for maintaining basic physical function, especially mobility such as walking and climbing stairs in older adults. It is well established that lower knee extensor strength is associated with increased risk of incident mobility limitations. [20-22] Although it is unclear whether there is a certain threshold level of leg strength per body weight to maintain physical function, it is obvious that lower muscle strength is definitely a risk factor for physical disability independent of lower muscle mass itself. [22]

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 close association of muscle strength and severity of diabetic neuropathy in the previous cross-sectional observations. [8-9] Electrophysiologic studies showed that muscle strength in diabetic patients correlated with fiber density and amplitude of the macro motor unit potential, suggesting incomplete reinnervation following axonal loss. [23] Longitudinal studies suggest an average loss of compound muscle action potential amplitude at a rate of ~3% per year in patients with type 2 diabetes over a 10-year period. [24] Unfortunately muscle strength was not assessed in their study. Future research should identify the role of the decrease in motor amplitudes on the 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 attenuated the declines in muscle strength only slightly. It suggests that chronic complications of diabetes have a limited role in the declines in the 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 of muscle function may indeed the result of diabetic neuropathy.

Another potential mechanism would be increased inflammatory cytokines in subjects with diabetes. It has been reported that systemic proinflammatory cytokines such as TNF-α and IL-6 have detrimental effects on muscle mass, strength and physical performance in older adults. [25-26] In our study, declines in muscle strength in older adults with diabetes are attenuated a little by adjusting for TNF-α and IL-6. However, the duration of diabetes and level of glycemic control reflected by baseline glycosylated hemoglobin did not explain the declines in muscular function (data not shown).

Our study has several limitations. The study population was well-functioning community-dwelling black and white men and women who were definitely healthier than those in the typical same-aged population. However, the purpose of the Health ABC Study was to identify factors related with incident functional limitations in those without disability at baseline. There were many drop-outs and only about 70% of participants were completed year three assessments. However, we believe that the lost to follow up may underestimate the true decline in muscle function in those with diabetes as described above and in table 12 and 13. Finally, we lacked information about neuropathy at baseline, which would be closely related with muscular function in diabetes.

In conclusion, the present study clearly showed an accelerated loss of knee extensor strength in older adults with type 2 diabetes. This result confirms previous cross-sectional finding of low muscle strength and quality in the same cohort and strongly suggest that poor muscle function in older adults is a consequence of diabetes rather than a coincidence.

Table 9. Characteristics of participants in the Health, Aging and Body Composition Study by diabetes status

	Without diabetes (n, 1,535)	With diabetes (n, 305)	P*
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
Peripheral artery disease	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, log (kcal/week)	3.7 ± 0.4	3.7 ± 0.4	0.418
Biochemical			
Fasting glucose (mg/dl)	93.0 ± 9.7	151.8 ± 52.2	<0.001
HbA1c (%)	6.0 ± 0.5	7.9 ± 1.6	<0.001
Interleukin-6† (pg/ml)	1.63 (1.12-2.44)	2.16 (1.47-3.08)	<0.001
Tumor necrosis factor-α† (pg/ml)	3.03 (2.35-3.86)	3.41 (2.57-4.37)	<0.001

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

Table 10. Three-year changes in skeletal muscle strength, mass and quality by diabetes status in the Health, Aging and Body Composition study

	Without diabetes (n, 1535)			With diabetes (n, 305)			P‡
	Baseline	36 months	Change	Baseline	36 months	Change	
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 <0.001 between baseline and 36 months within the same group
† P <0.01 versus those without diabetes at the same time period
‡ P-values for comparison of 3-yr changes between two groups

Table 11. Adjusted 3-year changes in knee extensor strength and muscle quality by diabetes status in the Health, Aging and Body Composition study

	Without diabetes n, 1535	With diabetes n, 305	P
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	-15.8 ± 1.1	0.008
Model 4	-12.7 ± 0.5	-15.6 ± 1.2	0.027
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	-1.63 ± 0.15	0.019

Data are adjusted means ± standard error
Model 1: adjusted for sex, race, age, and clinic site
Model 2: additionally adjusted for body mass index, baseline strength or quality, and changes in leg lean mass
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)

Table 12. Baseline characteristics of completers and incompleters in the Health, Aging and Body Composition Study

	Completers n, 1840 (70.3%)	Incompleters n, 778 (29.7%)	P
Age (years)	73.4 ± 2.8	73.9 ± 2.9	<0.001
Men (%)	50.3	53.5	0.135
Blacks (%)	36.1	49.4	<0.001
BMI (kg/m^2)	27.2 ± 4.5	27.7 ± 5.3	0.010
Diabetes (%)	16.6	23.1	<0.001
Coronary heart disease (%)	16.5	22.9	<0.001
Congestive heart failure (%)	1.7	5.8	<0.001
Stroke (%)	1.8	4.4	<0.001
Peripheral artery disease (%)	3.4	7.2	<0.001
Impaired vision (%)	18.1	24.4	<0.001
Renal insufficiency (%)	7.0	14.2	<0.001
Subclinical PAD (%)	11.0	18.3	<0.001
Knee extensor strength (Nm)	109.5 ± 38.2	98.6 ± 35.6	<0.001
Hand grip strength (kg)	32.5 ± 10.8	30.8 ± 10.8	<0.001
Reasons for incompletion (n, %)			
Death	-	146 (18.8)	
Home examination*	-	245 (31.5)	
Proxy interview*	-	57 (7.3)	
Contraindications for knee strength test†	-	191 (24.6)	
Missing data for DXA body composition	-	51 (6.6)	
Missed contact	-	77(9.9)	
Withdrawal		11 (1.4)	

Data are mean ± SD or proportions,

* The main reasons for home examination and proxy interview were participant's disabilities and/or institutionalization.

† Contraindications for knee strength test include uncontrolled hypertension, history of stroke or aneurism in the brain, bilateral knee joint replacement, and severe bilateral knee pain

Table 13. Characteristics of incompleters in the Health, Aging and Body Composition Study by diabetes status

	Without diabetes n, 598	With diabetes n, 180	P
Incompletion rate (% of initial participants)	28.0	37.1	<0.001
Age (years)	74.0 ± 2.9	73.7 ± 3.1	0.275
Men (%)	54.7	49.4	0.217
Blacks (%)	45.7	61.7	<0.001
BMI (kg/m^2)	27.3 ± 5.2	29.2 ± 5.4	<0.001
Coronary heart disease (%)	19.7	33.3	<0.001
Congestive heart failure (%)	4.2	11.1	<0.001
Stroke (%)	3.7	6.7	0.086
Impaired vision (%)	22.1	31.8	0.008
Renal insufficiency (%)	12.0	21.2	0.002
Subclinical PAD (%)	17.5	21.0	0.312
Knee extensor strength (Nm)	99.7 ± 36.3	94.9 ± 32.7	0.125
Hand grip strength (kg)	30.8 ± 11.1	30.6 ± 10.0	0.810
Changes in hand grip strength (kg)*	-1.1 ± 6.2	-3.3 ± 6.7	0.036

Data are mean ± SD or proportions

* Based on available data (n=181 for those without diabetes, and 47 for those with diabetes), year 3 hand grip strength was measured either at clinic or at home

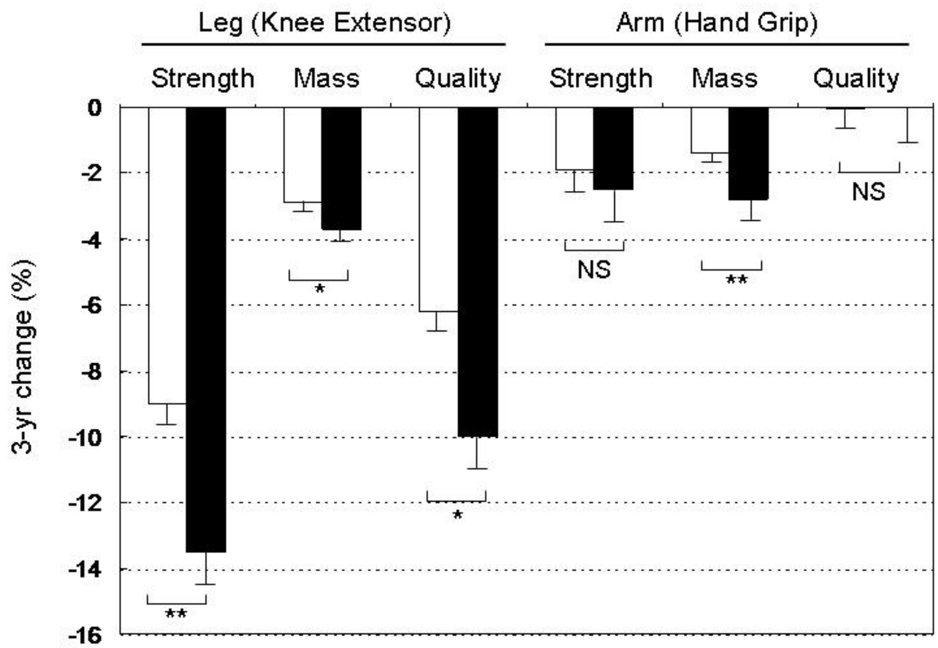

Figure 3. Mean (± SE) relative 3-yr changes in skeletal muscle strength, mass, and muscle quality in older adults with type 2 diabetes (■) and without diabetes (□). NS, not significant, * P <0.05, ** P < 0.01

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4. ARTICLE THREE: ACCELERATED LOSS OF SKELETAL MUSCLE MASS IN OLDER ADULTS WITH DIABETES MELLITUS: THE HEALTH, AGING AND BODY COMPOSITION STUDY

4.1 ABSTRACT

Loss of muscle mass (sarcopenia) is common in older adults. The aim of this study was to examine longitudinal changes of body composition in older adults in relation to diabetes (DM) status at baseline. We assessed body composition annually by dual energy X-ray absorptiometry over a five year period in 2,675 older adults in the Health, Aging and Body Composition Study. Diagnosed DM (n, 402) was identified by self-report or use of hypoglycemic agents. Undiagnosed DM (n, 226) was defined by fasting plasma glucose ≥ 126 mg/dL or 2-hour post-challenge plasma glucose ≥ 200 mg/dL among those without diagnosed DM. We also measured body fat distribution and thigh muscle area by computed tomography at the L4-L5 disc space and mid-thigh at baseline and 5 years later. Longitudinal regression models were fit to examine the impact of diabetes on the annual changes in body composition adjusting for age, sex, race, clinic site, baseline body composition, and weight loss intention assessed by questionnaire at each year. Both diagnosed DM and undiagnosed DM showed accelerated loss of appendicular lean mass and trunk fat mass compared with non-diabetic older adults. Furthermore, thigh muscle area declined two times faster in older women with diagnosed DM and undiagnosed DM than non-diabetic women. These findings are independent of baseline body composition, weight change, and inflammatory cytokines. In conclusion, diabetes is associated with accelerated loss of skeletal muscle mass in older adults. Older women with undiagnosed DM are at especially high risk for loss of skeletal muscle mass.

4.2 INTRODUCTION

Weight loss occurs frequently in older adults and it has been associated with increased morbidity and mortality. [1-3] In older persons, weight loss is strongly associated with loss of lean mass although they would be expected to lose both lean and fat mass. [4-6] Even in weight stable older adults, there is a background loss of lean mass. [7] An excessive loss of lean mass would result in loss of skeletal muscle strength, mobility limitations, disability, and eventually high mortality in older adults. [8-11] However, little is known about the causes or risk factors associated with weight loss and loss of lean mass in older adults. Obesity and changes in body composition, especially accumulation of abdominal fat, is an important risk factor for type 2 diabetes. [12-14] But, the changes in weight and body composition after the development of diabetes are not well studied.

In a large, ongoing cohort study of older black and white men and women, the Health, Aging, and Body Composition (Health ABC) Study, we assessed changes in total mass, fat free non-bone lean mass, and fat mass over 5 years with precise measures of total and regional body composition with state of the art techniques such as dual-energy X-ray absorptiometry (DXA) and computed tomography (CT). The aim of this study was to investigate longitudinal changes in total and regional body composition in relation to baseline diabetes status in well-functioning community-dwelling older adults. We hypothesized that older adults with type 2 diabetes, particularly those with undiagnosed diabetes, might show an accelerated loss of skeletal muscle mass.

4.3 METHODS

4.3.1 Participants

The Health ABC Study is a longitudinal investigation of the relation between changes in body composition and functional decline with aging. The study cohort consisted of 3,075 well functioning black and white men and women aged 70 to 79 years (men: 48%, black: 42%). Whites were recruited from a random sample of Medicare beneficiaries residing in ZIP codes from the metropolitan areas surrounding Pittsburgh, Pennsylvania and Memphis, Tennessee. Blacks were recruited from all age-eligible residents in these geographic areas. Eligibility criteria included: age 70 to 79 years old in the recruitment period from March 1997 to July 1998; self-report of no difficulty walking one-quarter of a mile or climbing 10 steps without resting; no difficulty performing basic activities of daily living; no reported use of a cane, walker, crutches or other special equipment to ambulate; no history of active treatment for cancer in the prior 3 years; and no plan to move out of the area in the next 3 years.

Of the 3,075 participants, 2,675 older adults (87%) who had body composition assessments by DXA at baseline and at least one more annual follow-up were included for this study. The changes in body composition were assessed for 11,873 person years. The average follow up duration was 4.4 years. The majority of participants took annual DXA scans for more than 4 years [1,961 (73%) for 6 years, 273 (10%) for 5 years, 157 (6%) for 4 years]. The main reason for lost to follow up examination was death of participants (519, 19 %) through year 6. A subgroup of participants (1,629, 53% of original cohort) who had assessment of mid-thigh muscle area by CT at both year 1 (baseline) and year 6 was analyzed separately.

4.3.2 Assessment of diabetes

Participants were considered as having diagnosed diabetes if they had either a report of physician diagnosed diabetes mellitus or current use of a hypoglycemic medication. We performed 75g oral glucose challenge test for all participants except those with diagnosed diabetes. Undiagnosed diabetes was defined by a fasting plasma glucose concentration level of 126 mg/dL or greater (≥ 7.0 mmol/L), or a 2-hour post-challenge plasma glucose level of 200 mg/dL or greater (≥ 11.1 mmol/L) among those without diagnosed diabetes. The average duration of diabetes for diagnosed diabetes was 13.3 ± 10.9 years from the time of diagnosis. Plasma glucose was measured using an automated glucose oxidase reaction (Vitros 950 analyzer, Johnson and Johnson, Rochester, NY) and a glycosylated hemoglobin (HbA_{1c}) was measured by enzymatic method (Bio-Rad, Hercules, CA).

4.3.3 Body composition by DXA

Body weight and height were measured in a hospital gown and without shoes on a calibrated balance beam scale and stadiometer, respectively, and a body mass index (BMI) in kg/m^2 was calculated. We used fan-beam dual energy x-ray absorptiometry (model QDR 4500, software version 8.21, Hologic, Bedford, MA) to measure total body mass and body composition. Total body fat and lean mass were measured and separated into trunk and appendicular components. Bone mineral content was subtracted from the total and regional lean mass to define total and regional non-bone lean mass. Appendicular lean mass was calculated as the sum of lean soft tissue (non-fat, non-bone) mass in the arms and legs, which represents primarily skeletal muscle mass in the extremities. The validity and reproducibility of the body composition data in the Health ABC Study were reported previously. [15-17] Quality-assurance measures included the use of a body composition phantom for calibration and annual assessment for potential site differences or drift over time.

4.3.4 Body composition by CT

Axial CT scans at the abdomen and mid-thigh level was obtained at baseline (year 1) and five years later (year 6). CT images were acquired either in Pittsburgh (9800 Advantage; General Electric, Milwaukee, WI) or Memphis (Somaton Plus [Simens, Iselin, NJ] or PQ2000S [Picker, Cleveland, OH]). Skeletal muscle and adipose tissue areas of the thigh were calculated from the axial CT images using proprietary IDL development software (RSI Systems, Boulder, CO). The adipose tissue interspersed between muscle, termed intermuscular fat, was distinguished from the subcutaneous fat by manually drawing a line along the deep fascial plane surrounding the thigh muscles. We used mid-thigh muscle cross sectional area as an indicator of skeletal muscle mass. To ensure the reproducibility and quality of the repeated CT scans, we performed a strict quality control: scans with any artifacts or poor quality were removed; abdominal scans obtained at or above L3/L4 level or at or below L5/S1 level were removed; mid-thigh scans obtained from different leg or a slice location on the femur greater than 2 cm of the baseline scan were also removed.

4.3.5 Inflammatory cytokines

Interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) were measured in duplicate using an untrasensitive enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, Minn). The lower limit of detection was less than 0.10 pg/ml for IL-6 and 0.18 pg/ml for TNF-α, with coefficients of variation of 6.3% and 16.0%, respectively.

4.3.6 Statistical analysis

Baseline characteristics of the cohort are presented separately for three groups defined by baseline diabetes status. Analysis of variance tests, Chi-square tests, or Kruskal Wallis tests were used to examine differences in the descriptive characteristics of the study population. The longitudinal changes in body composition were analyzed by the generalized estimating equations (with SAS Version 8.1 Proc Genmod) developed by Liang and Zeger (18-19). This method simultaneously examines the cross-sectional relation between each independent variable and body composition and the longitudinal relation between these variables and changes in body composition over time. Included in the models are potential confounding factors which are associated with body composition and its changes over time. The initial model included age, sex, race, clinic site, baseline body composition, weight loss intention at each year, two dummy variables for diagnosed DM and undiagnosed DM, examination year (Yr) as a time-dependent covariate, and cross-product terms between Yr and two dummy variables for diabetes (Yr*diagnosed DM, Yr*undiagnosed DM) to assess changes in body composition over time between groups. Interactions with sex, race, clinic site with diabetes variables (eg. sex*diagnosed

DM*Yr) were assessed. There was no significant interaction effect ($p<0.10$) between sex, race, or clinic site with diabetes variables on the changes in body composition. The final model included changes in body weight at each examination year as time-dependent covariates to examine effects of diabetes on the changes in each body composition parameters adjusting for body weight changes.

For the body composition data obtained from CT scan, changes in abdominal subcutaneous fat, visceral fat, thigh subcutaneous fat, thigh intermuscular fat, and thigh muscle cross-sectional area were calculated in both absolute terms (year 6 value minus year 1 value) and relative terms (percent change from baseline). Differences between groups were assessed by general linear models controlling for age, sex, race, clinic site, and baseline values when using absolute changes. We found a significant interaction effect ($p<0.05$) of sex and diabetes variables on the changes of thigh muscle area. Therefore, further analyses were stratified by sex for CT data. Additional adjustments were made for baseline body composition, weight change, IL-6 and TNF-α. We used Bonferroni correction methods for multiple comparisons between groups. A p-value of <0.05 was accepted as statistically significant. The analyses were performed using SPSS (version 12.0.0, SPSS Inc., Chicago, IL) and SAS (version 8.1, SAS Institute, Inc., Cary, NC).

4.4 RESULTS

Among the 2,675 participants with follow-up body composition assessments with DXA, 402 (15.0%) had diagnosed diabetes at baseline. Two hundred twenty six older adults (8.5%) were undiagnosed diabetes identified by a result of oral glucose challenge test. Those with either diagnosed or undiagnosed diabetes were more likely to be men, black, and had higher BMI, total body mass (weight), total fat and total lean mass than those without diabetes (Table 1). As expected, coronary heart disease, congestive heart failure, stroke, impaired vision, and renal insufficiency were more prevalent in those with diagnosed diabetes. IL-6 and TNF-α levels were significantly higher in older adults with either diagnosed or undiagnosed diabetes (Table 14).

Total body mass (weight), total and appendicular lean mass declined with aging in all three groups. However, the slopes of decline were steeper in those with undiagnosed diabetes (Figure 4). Total fat mass increased or maintained in those without diabetes and those with diagnosed diabetes, whereas it declined slightly in those with undiagnosed diabetes. The annual changes in each body composition parameters adjusting for age, sex, race, clinic site, baseline body composition, and weight loss intention at each year are summarized in Table 15. In older adults with undiagnosed diabetes, the loss of total and appendicular lean mass were significantly greater than those without diabetes ($p<0.01$). They also showed greater loss of trunk lean mass ($p<0.01$), total and trunk fat mass ($p<0.05$) compared with non-diabetic older adults. Those with diagnosed diabetes showed greater loss of appendicular lean and trunk fat mass compared with non-diabetic older adults ($p<0.05$). Table 16 shows disproportional changes in body composition adjusting for body weight changes. In all three groups, lean body mass decreased and fat mass increased over time after adjusting for weight change. In other words, there were significant loss of lean mass and accumulation of fat mass accounting for the changes in overall body weight. Furthermore, the declines of total and appendicular lean mass in older adults with undiagnosed diabetes were greater than non-diabetic older adults adjusting for age, sex, race, clinic site, baseline body composition, weight loss intention, and changes in body weight. In older adults with diagnosed diabetes, trunk lean and fat mass were slightly increased when the changes in overall weight were accounted for (Table 16).

Five year changes in body composition assessed by CT scan were summarized in Table 17. The changes in abdominal subcutaneous fat, visceral fat, thigh subcutaneous fat, and intermuscular fat area were not different between groups. However, thigh muscle area was decreased more rapidly in older women with either diagnosed or undiagnosed diabetes than those without diabetes (Table 17). There was a significant interaction effect of sex and diabetes status on the changes in thigh muscle area ($p=0.044$). When the changes were assessed in relative term, older women with either diagnosed or undiagnosed diabetes showed twofold excess declines in thigh muscle area than non-diabetic women (Figure 5). In women, adjustments for baseline weight, weight change over 5 years, IL-6, and TNF-α slightly attenuated the rapid declines in thigh muscle area (Table 18). Older women with either diagnosed or undiagnosed diabetes remained to show about twofold greater loss of thigh muscle area even in fully adjusted model.

4.5 DISCUSSION

We found rapid declines in appendicular lean mass in older adults with diabetes, especially in undiagnosed cases. Furthermore, these declines were independent of changes in body weight itself, suggesting an excess and accelerated loss of skeletal muscle mass in older adults with diabetes. The CT data confirmed rapid loss of thigh muscle mass in older adults with diabetes although it was significant only in women.

In older adults, weight loss is a profound marker for devastating consequences such as physical disability and high mortality risk. [1-3] Adverse outcomes of weight loss in older adults may be attributable to an excessive loss of lean mass and resultant sarcopenia. [6] The findings of our study clearly show that diabetes in older adults is associated with excessive loss of appendicular lean mass, which represents loss of primarily skeletal muscle mass. Interestingly, older adults with undiagnosed diabetes are particularly at high risk for loss of lean mass. There is a paucity of literature in this area. To our knowledge, this is the first study showing excessive loss of lean mass in older adults with diabetes. Diabetes mellitus was one of factors associated with weight loss in 4,714 community-dwelling adults aged 65 and older in the Cardiovascular Health Study (CHS). [3] However, lean body mass was not assessed in CHS and we did not know which body composition was responsible for weight loss in older adults with diabetes.

It has been known that changes in lean body mass are strongly coupled with changes in body weight. [4-5, 21] But, in older adults, significantly more lean mass is lost with weight loss than is gained with weight gain. [6] Even in weight stable individuals, there is a background loss of lean mass suggesting that loss of lean mass or sarcopenia is a progressive process with aging. [7] Excessive loss of lean mass has been observed particularly in elderly men. In our study, there was no interaction effect of sex and baseline diabetes status on the changes in total and appendicular lean mass assessed by DXA. We found the same results even if the analyses were stratified by sex for changes in lean mass assessed by DXA (data not shown). However, we found a significant interaction effect of sex and diabetes status on the changes in thigh muscle area assessed by CT scan. Older women with either diagnosed or undiagnosed diabetes showed about twofold excessive loss of thigh muscle area compared with non-diabetic women. In fact, the rate of thigh muscle decline in older women with diabetes was almost the same as older men suggesting that women with diabetes lost beneficial effect of female sex on preserving lean mass (Figure 5). Previous studies showed that loss of lean mass was greater in men than women. [6, 20-21] Higher background decline rate of thigh muscle area in older men without diabetes may make it difficult to detect the changes associated with diabetes. It is also possible that survival bias or selection bias for year 6 CT measurement may obscure the true association, particularly in men. In our cohort, lost to follow-up for year 6 CT measurement was non-random because older adults with diabetes had higher mortality rate, especially in men (5-yr mortality rates: 21.4% vs 32.5% vs 30.5% for men, p=0.001 and 12.6% vs 13.0% vs 21.2% for women, p=0.008; for those without diabetes, those with undiagnosed diabetes, and those with diagnosed diabetes, respectively). Failure to return to the clinic visit due to disability and institutionalization was also higher in older adults with diabetes. Our previous report on the changes of muscle strength in the same population suggested that this differential follow-up rate or non-random missing biased the result to the null. The longitudinal analyses by generalized estimating equation have advantages for reducing selection bias because it uses all available data from annual measurements of body composition. Generalized estimating equation allows missing measurements during follow-up instead of eliminating the individuals with missing data. [22-23]

From the DXA data, an excessive loss of appendicular lean mass was evident in both diagnosed and undiagnosed diabetes. Interestingly, those with undiagnosed diabetes showed the greatest decline in appendicular lean mass suggesting undiagnosed diabetes is a significant risk factor for loss of muscle mass and sarcopenia. Long duration of exposure to diabetes (average 13.3 years) may already affect the baseline body composition in older adults with diagnosed diabetes, which make it difficult to detect any further changes in body composition. It is also possible that treatment effects can modify the association of diabetes and changes in body composition. For example, insulin therapy usually results in weight gain. A subgroup analyses for the influence of various treatments in older adults with diagnosed diabetes will be an interesting topic and we are now in progress to answer this question.

The reason for an accelerated loss of lean mass in older adults with undiagnosed diabetes is unknown for now. Increased inflammatory cytokines are possibly involved in this process, because diabetes has been known to be subclinical inflammatory status [24-25] and elevated inflammatory cytokines are associated with muscle mass and physical performance in older persons. [26-28] However, in our study, the adjustments for IL-6 and TNF-α only slightly attenuated the declines in thigh muscle area. It is also possible that older adults with undiagnosed diabetes were trying to lose weight intentionally because we informed the result of oral glucose challenge test to the participants in the Health ABC Study. However, excess loss of lean mass was evident even after adjusting for the weight loss intention assessed by questionnaire at each examination year. In fact, weight loss intention did not result in actual weight loss in our cohort (data not shown).

It can be postulated that metabolic abnormalities of undiagnosed diabetes affect negatively on muscle mass. Metabolic derangements in diabetes relate mostly to hyperglycemia and to the catabolic state of the patient such as urinary loss of glucose and calories, muscle breakdown due to protein degradation and decreased protein synthesis. [29] Unexplained weight loss is, in fact, one of common manifestations of undiagnosed diabetes mellitus. To test whether loss of lean mass were related to the level of hyperglycemia, we are going to investigate the association between level of glycosylated hemoglobin (HbA1c) and changes in lean mass within this cohort.

The results of this study may have important public health implication. The prevalence of diabetes is increasing especially in older adults and about one third of diabetes is remained undiagnosed. [30-32] If older adults with undiagnosed diabetes were left untreated they would be at high risk for weight loss, particularly loss of lean mass. It seems highly likely that accelerated loss of lean mass in older adults with diabetes might be related to muscle strength loss, functional limitations, and physical disability. [33-36] Future research should find factors related with accelerated loss of lean mass in older adults with diabetes to develop strategies to prevent sarcopenia in this high risk population. [37-38] In conclusion, diabetes mellitus is associated with accelerated loss of skeletal muscle mass in older adults. Those with undiagnosed diabetes are at especially high risk for loss of skeletal muscle mass.

Table 14. Characteristics of participants by baseline diabetes status

	Without diabetes (n,2047)	Undiagnosed diabetes (n, 226)	Diagnosed diabetes (n, 402)	P*
Sociodemographic				
Age (years)	73.6 ± 2.9	73.7 ± 2.8	73.6 ± 2.7	NS
Men (%)	47.6	55.8	55.5	<0.001
Blacks (%)	36.7	42.0	57.7	<0.001
Body Composition				
BMI (kg/m^2)	26.8 ± 4.6	28.5 ± 4.8	29.1 ± 4.7	<0.001
Total body mass (kg)	74.2 ± 14.4	79.9 ± 15.8	81.2 ± 14.0	<0.001
Total lean mass (kg)	45.9 ± 9.8	49.1 ± 10.3	50.4 ± 9.3	<0.001
Trunk lean	23.1 ± 4.8	24.8 ± 5.1	25.3 ± 4.7	<0.001
Appendicular lean	19.8 ± 4.9	21.1 ± 5.1	21.9 ± 4.6	<0.001
Total fat mass (kg)	26.0 ± 8.4	28.4 ± 9.0	28.5 ± 8.7	<0.001
Trunk fat	12.9 ± 4.6	14.9 ± 5.3	15.0 ± 5.0	<0.001
Appendicular fat	12.6 ± 4.5	13.0 ± 4.6	12.8 ± 4.3	NS
Chronic diseases				
Coronary heart disease (%)	18.0	24.3	27.1	<0.001
Congestive heart failure (%)	2.0	5.8	4.5	<0.001
Stroke (%)	7.3	6.6	11.2	<0.05
Knee osteoarthritis (%)	8.5	7.5	7.2	NS
Depression (%)	11.9	11.1	11.2	NS
Cancer (%)	19.8	22.1	16.2	NS
Impaired vision (%)	18.6	18.2	27.4	<0.001
Renal insufficiency (%)	8.3	7.5	17.4	<0.001
Behavioral factors				
Current smoking (%)	10.4	8.0	9.0	NS
Alcohol drinking (%)	53.2	55.8	30.8	<0.001
Physical activity, (kcal/kg/week)	87.2 ± 68.7	77.9 ± 62.3	75.0 ± 75.0	0.002
Biochemical				
Fasting glucose (mg/dl)	92.6 ± 9.4	125.7 ± 39.5	154.1 ± 58.6	<0.001
HbA1c (%)	6.0 ± 0.5	6.9 ± 1.3	8.0 ± 1.6	<0.001
Interleukin-6† (pg/ml)	1.72 (1.17-2.62)	2.10 (1.38-3.08)	2.16 (1.52-3.19)	<0.001
Tumor necrosis factor-α† (pg/ml)	3.08 (2.38-3.95)	3.28 (2.49-4.34)	3.46 (2.58-4.42)	<0.001

Data are mean ± SD, proportions, or median (interquartile range).
* P values from analysis of variance or chi-square tests. † Kruskal Wallis tests.

Table 15. Annual changes in body composition variables assessed with dual-energy X-ray absorptiometry by baseline diabetes status

	Without diabetes (n,2047)	Undiagnosed diabetes (n, 226)	Diagnosed diabetes (n, 402)
Total body mass (g/yr)	-189 (23)	-441 (80)**	-279 (72)
Total lean mass (g/yr)	-196 (10)	-340 (37)**	-216 (29)
Trunk lean (g/yr)	-42 (6)	-105 (22)**	-27 (16)
Appendicular lean (g/yr)	-149 (5)	-225 (20)**	-184 (16)*
Total fat mass (g/yr)	27 (16)	-93 (53)*	-61 (53)
Trunk fat (g/yr)	46 (10)	-41 (35)*	-32 (32)*
Appendicular fat (g/yr)	-15 (7)	-49 (24)	-27 (24)

Data are β-coefficients (SE) estimated by generalized estimating equations adjusting for age, sex, race, clinic site, baseline body composition, and weight loss intention at each year
* $p < 0.05$, ** $p < 0.01$ versus those without diabetes

Table 16. Disproportional changes in body composition variables after adjusting for changes in body weight by baseline diabetes status

	Without diabetes (n,2047)	Undiagnosed diabetes (n, 226)	Diagnosed diabetes (n, 402)
Total lean mass (g/yr)	-125 (7)	-187 (25)*	-101 (19)
Trunk lean (g/yr)	-9 (5)	-33 (18)	27 (13)*
Appendicular lean (g/yr)	-113 (4)	-149 (14)*	-130 (11)
Total fat mass (g/yr)	164 (7)	204 (23)	155 (20)
Trunk fat (g/yr)	126 (5)	135 (18)	95 (14)*
Appendicular fat (g/yr)	42 (4)	74 (14)*	60 (12)

Data are β-coefficients (SE) estimated by generalized estimating equations adjusting for age, sex, race, clinic site, baseline body composition, weight loss intention at each year, and changes in body weight
* $p < 0.05$ versus those without diabetes.

Table 17. Five-year changes in body composition variables assessed with computerized tomography by baseline diabetes status, stratified by sex

	Without diabetes			Undiagnosed diabetes			Diagnosed diabetes		
	Baseline	Change	% change	Baseline	Change	% change	Baseline	Change	% change
Men		(n, 606)			(n, 68)			(n, 120)	
Abdomen									
Subcutaneous fat area (cm^2)	223.8 ± 3.5	-14.0 ± 1.6	-5.8 ± 0.8	246.2 ± 12.3	-16.4 ± 4.8	-7.8 ± 2.0	250.2 ± 8.4*	-14.2 ± 5.2	-5.1 ± 2.0
Visceral fat area (cm^2)	152.9 ± 2.8	-1.1 ± 1.8	-1.0 ± 1.2	187.4 ± 10.1*	3.6 ± 6.8	1.9 ± 4.0	173.0 ± 6.8*	-0.1 ± 5.2	3.5 ± 3.0
Mid-thigh									
Subcutaneous fat area (cm^2)	95.8 ± 1.6	-2.0 ± 0.7	-2.0 ± 0.8	94.4 ± 4.7	-2.5 ± 2.4	-3.6 ± 2.8	93.6 ± 3.4	1.2 ± 2.0	0.8 ± 2.0
Intermuscular fat area (cm^2)	18.7 ± 0.4	6.0 ± 0.2	48.9 ± 2.4	21.1 ± 1.5	6.4 ± 0.7	41.4 ± 4.9	21.6 ± 1.6	7.6 ± 0.6*	51.6 ± 4.1
Muscle area (cm^2)	262.5 ± 1.7	-12.9 ± 0.7	-4.8 ± 0.3	271.7 ± 5.2	-18.2 ± 2.7	-6.4 ± 0.9	273.5 ± 3.8*	-14.4 ± 2.0	-5.2 ± 0.7
Muscle attenuation (HU)	37.7 ± 0.3	-0.9 ± 0.2	-1.0 ± 0.6	36.8 ± 0.7	-1.7 ± 0.6	-4.3 ± 1.7	37.5 ± 0.2	-1.7 ± 0.6	-3.2 ± 1.6
Women		(n, 684)			(n, 57)			(n, 94)	
Abdomen									
Subcutaneous fat area (cm^2)	327.3 ± 4.6	-24.0 ± 2.0	-7.1 ± 0.8	358.9 ± 15.1	-26.8 ± 6.4	-8.1 ± 1.9	371.8 ± 11.6*	-27.2 ± 7.6	-7.0 ± 1.9
Visceral fat area (cm^2)	122.6 ± 2.1	-9.5 ± 1.3	-7.6 ± 1.0	157.3 ± 8.9*	-8.6 ± 3.9	-7.4 ± 3.0	165.7 ± 6.7*	-19.6 ± 4.7*	-10.4 ± 3.0
Mid-thigh									
Subcutaneous fat area (cm^2)	211.5 ± 3.4	-6.9 ± 1.2	-2.7 ± 0.6	224.6 ± 12.5	-8.2 ± 5.0	-1.6 ± 2.3	218.2 ± 9.4	-5.6 ± 4.5	-0.8 ± 2.2
Intermuscular fat area (cm^2)	19.3 ± 0.5	3.4 ± 0.2	30.4 ± 1.6	22.3 ± 1.5	3.5 ± 1.0	24.3 ± 5.3	25.4 ± 1.4*	3.7 ± 0.7	24.8 ± 3.9
Muscle area (cm^2)	181.7 ± 1.3	-4.9 ± 0.5	-2.5 ± 0.3	194.1 ± 4.7*	-12.0 ± 2.8*	-5.5 ± 1.3*	206.8 ± 3.4*	-12.0 ± 1.9*	-5.5 ± 0.9*
Muscle attenuation (HU)	34.4 ± 0.3	-0.3 ± 0.2	0.7 ± 0.7	32.9 ± 0.9	-0.8 ± 0.8	-1.4 ± 0.3	33.5 ± 0.7	-0.4 ± 0.6	-1.7 ± 0.3

Data are adjusted means ± SE from general linear models adjusting for age, sex, race, and clinic site.
* P <0.05 versus those without diabetes, after Bonferroni correction for multiple comparisons

Table 18. Multivariate models for 5-year changes in thigh muscle cross sectional area by baseline diabetes status in older women

	Without diabetes	Undiagnosed diabetes	Diagnosd diabetes	P
Model 1	-5.1 (0.5)	-11.7 (1.8)*	-11.1 (1.4)*	<0.001
Model 2	-5.2 (0.5)	-11.3 (1.8)*	-10.6 (1.4)*	<0.001
Model 3	-5.3 (0.4)	-10.8 (1.4)*	-10.0 (1.1)*	<0.001
Model 4	-5.2 (0.4)	-10.6 (1.5)*	-9.3 (1.2)*	<0.001

Data are adjusted means (SE)
Model 1: adjusted for age, race and clinic site
Model 2: additionally adjusted for baseline body weight
Model 3: additionally adjusted for changes in body weight
Model 4: additionally adjusted for interleukin-6 and tumor necrosis factor-α
* p <0.01 versus those without diabetes, after Bonferroni correction for multiple comparison.

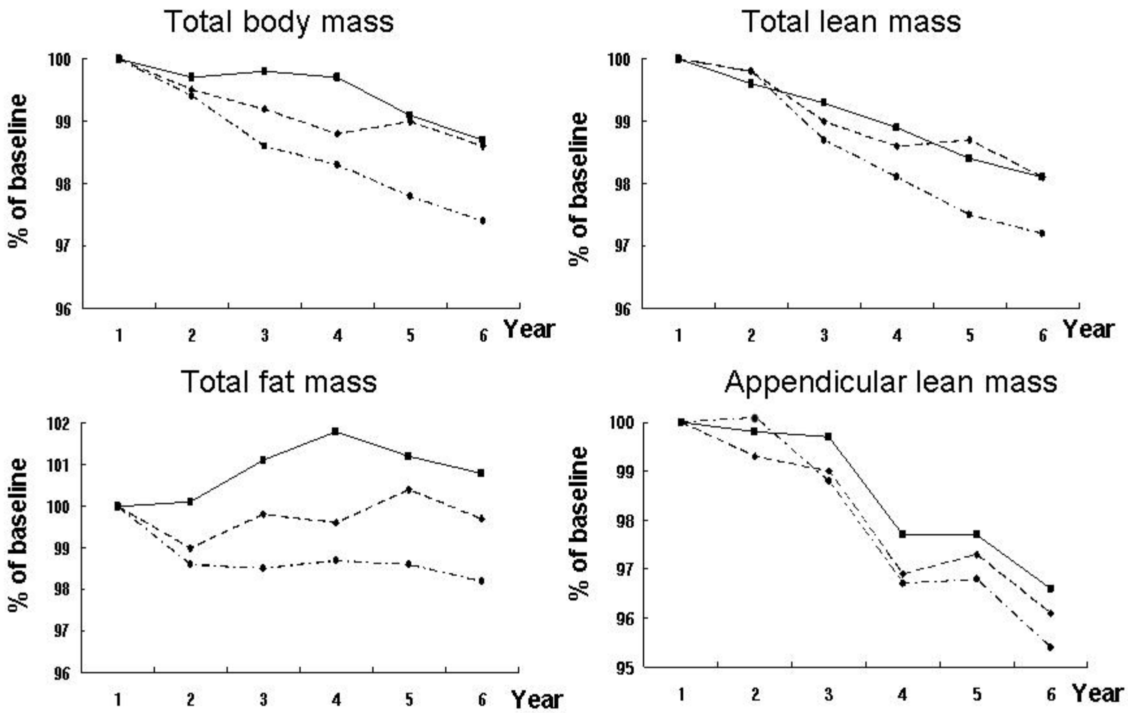

Figure 4. Longitudinal changes in body composition by baseline diabetes status in the Health, Aging and Body Composition Study.
(■——■ without diabetes, ●-·-·-● undiagnosed diabetes, ♦------♦ diagnosed diabetes)

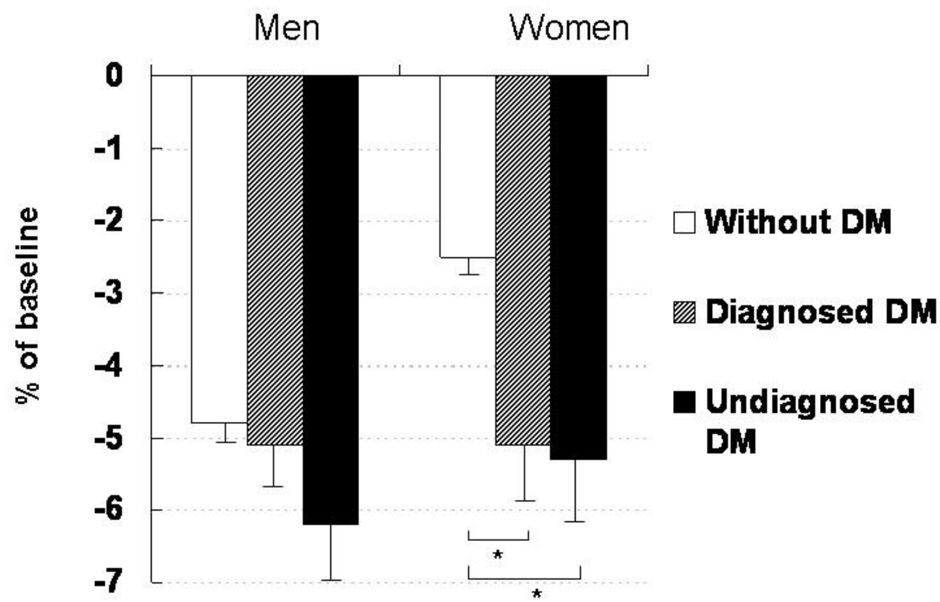

Figure 5. 5-yr relative changes in thigh muscle area by baseline diabetes Status, stratified by sex, in the Health, Aging and Body Composition Study. Adjusted for age, race, and clinic site.
*p<0.01 after Bonferroni correction.

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5. DISCUSSION

This cross-sectional and longitudinal study of the association between diabetes in older adults and skeletal muscle phenotypes including muscle quantity and function clearly shows that diabetes is a risk factor for loss of muscle mass and strength. We demonstrated not only a cross-sectional association but also dose-response effects of diabetes duration and severity, reflected by high glycosylated hemoglobin (A1c), on skeletal muscle quality defined as maximal strength per unit muscle mass. Furthermore, this cross-sectional association was confirmed by longitudinal data showing a temporal relationship between diabetes and loss of muscle mass and strength.

The Health, Aging, and Body Composition (Health ABC) Study is an ideal cohort to examine the impact of diabetes on body composition and muscle strength because we measured body composition annually up to 6 years by state of the art techniques such as dual-energy X-ray absortiometry and computed tomography. We were able to assess muscle quality, which represents contractile capacity of skeletal muscle groups because maximal muscle strength was measured quantitatively by isometric and isokinetic dynamometer. Moreover, we could identify many undiagnosed diabetes by a 75g-oral glucose challenge test performed for all participants without history of diabetes. We also collected extensive information on baseline sociodemographic variables, past medical history (adjudicated by self-reported physician-diagnosed diseases, medication use, and clinic assessment), and various lifestyle factors (smoking, alcohol drinking, physical activity, and intention to lose weight, etc.) in the Health ABC Study. Therefore we were able to adjust potential factors which might confound the associations between diabetes and muscle mass and strength in our cohort.

To our knowledge, this is the first study showing that diabetes is clearly associated with rapid loss of muscle mass and strength in older adults. Our findings have important public health implications because the prevalence of diabetes is continuously increasing especially in older population and diabetes in older adults is an established risk factor of developing functional disability and mortality.

5.1 MUSCLE MASS IN DIABETES

In this study, older adults with diabetes had a greater amount of muscle mass in their arm and leg than those without diabetes at baseline. But it is just because persons with diabetes had higher BMI. Although older adults with diabetes had greater muscle mass in absolute amount, their muscle mass may be similar or possibly lower in relative terms than non-diabetic older adults. Previous cross-sectional study of the Health ABC cohort revealed some distinctive patterns of body composition in older adults with diabetes. [1] Older men and women with diabetes had higher % body fat, higher visceral and intermuscular fat, and lower muscle attenuation value than non-diabetic counterparts. Many older adults with diabetes are likely to have "sarcopenic obesity" because the proportion of fat free mass (% fat free mass) is lower than non-diabetic older adults. [1] It is also possible that DXA may overestimate the actual muscle mass in those with diabetes. DXA could not distinguish adipose tissue infiltrated within muscle mass from actual muscle mass. Lower muscle attenuation by CT scan may indirectly support this possibility because reduced muscle attenuation is a marker of an augmented fat infiltration within muscle. [2-3] Furthermore, lower muscle attenuation is associated with lower specific torque (maximal torque per unit muscle mass) in the Health ABC Study. [4]

Sarcopenia was originally defined by Baumgartner et al. [5] as appendicular skeletal muscle mass/height-squared (aLM/ht^2 in kg/m^2) being less than two standard deviations below the mean of a young reference group. But, it has been argued that alternative definition of sarcopenia such as appendicular lean mass adjusted for height and body fat mass by residuals is more strongly associated with lower extremity functional limitations. Therefore, as Newman et al. [6] suggested, fat mass should be considered in estimating sarcopenia especially in women and in overweight and obese individuals. In fact, Baumgartner's definition could not identify sarcopenic subjects in obese elderly subjects when 12-15% of obese people were classified as sarcopenia by Newman's definition. Furthermore, sarcopenia by Newman's definition was more closely associated with lower extremity limitations than sarcopenia by Baumgartner's definition. [6] Villareal et al. also showed that the percent body weight as fat-free mass was lower in obese elderly persons than non-obese non-frail subjects and non-obese frail subjects matched for age and sex. [7] In their study, despite a higher absolute amount of fat-free mass in the obese elderly, these subjects had lower muscle quality, poor functional performance, lower aerobic capacity, and reduced walking speed. Thus, these obese elderly adults had sarcopenia (low relative muscle mass and low muscle quality) despite having higher absolute amount of muscle mass. Sarcopenic obesity also predicts disability in instrumental activities of daily living (IADL) in the elderly. [8] The risk for incident disability in IADL was two to three times higher in sarcopenic obese subjects than non-sarcopenic obese subjects. [8] Unfortunately, the prevalence of sarcopenic obesity and its functional outcomes have never been studied in older adults with diabetes. This issue should be studied in the near future because the three greatest epidemiological trends of our times are the aging of the population and the epidemics of obesity and diabetes. [9]

In any case, our study clearly revealed that older adults with diabetes lost excess amount of their muscle mass than non-diabetic adults in a longitudinal analysis. To our knowledge, this is the first study showing that diabetes is a risk factor for sarcopenia in older adults. It seems likely that diabetes may confer susceptibility to lose muscle mass independently of obesity and overall weight loss because an excess loss of muscle mass in our study is evident even after adjusting for baseline body composition and changes in body weight. In our study, older adults with either undiagnosed or diagnosed diabetes had higher rates of weight loss intention assessed at each examination year. (Table 19). However, adjustments for weight loss intention did not attenuate excess loss of muscle mass in older adults with diabetes. The assessment of weight loss intention is very subjective because it is usually based on a questionnaire like "At the present time, are you trying to lose weight?" (yes/no). We found that weight loss intention changed each year with moderate to poor agreements between examination years (Table 20). In fact, actual weight changes up to 5 years were not different between participants intending and not intending to lose weight in our cohort (Table 21). [10] Moreover, in the Health ABC Study, the incidence of mobility limitation was not lower, but actually increased in older adults with intentional weight loss, especially in overweight (HR, 1.59; 95% CI, 1.12-2.25) and obese subjects (HR, 1.12; 95% CI, 0.70-1.79). [11] Not all, but some studies showed that intentional weight loss was associated with a reduced risk of all-cause mortality in middle aged adults. [12-14] However, in older adults, it is still unclear whether intentional weight loss is beneficial or not. This thesis is not designed to answer the above question. In the future, the issue of intentional weight loss should be explored in relation to muscle mass, strength and/or quality as well as physical function, disability, and mortality in older adults.

Table 19. Rates (%) of having weight loss intention at each year by baseline diabetes status

Examination year (n)	No diabetes	Undiagnosed diabetes	Diagnosed diabetes	P value (X^2 test)
Year 1 (2,673)	24.7	33.6	31.7	0.001
Year 2 (2,510)	30.8	41.7	35.0	0.003
Year 3 (2,357)	27.2	34.7	28.8	0.083
Year 4 (2,234)	29.2	30.6	31.1	0.758
Year 5 (2,129)	27.5	28.5	28.6	0.893
Year 6 (1,961)	26.1	29.2	30.1	0.306

Table 20. Measures of agreement in weight loss intention assessed by questionnaire at each year

Examination years	Kappa statistics	P-value
Year 1 and 2	0.448	<0.01
Year 1 and 3	0.414	<0.01
Year 1 and 4	0.383	<0.01
Year 1 and 5	0.374	<0.01
Year 1 and 6	0.344	<0.01

Table 21. Actual changes in body weight up to 5 years by weight loss intention

Intervals (n)	Changes in weight (kg)		P
	Weight loss not intended	Weight loss intended	
Years 1-2 (2,730)	-0.31 ± 2.92	-0.36 ± 3.19	NS
Years 1-3 (2,540)	-0.35 ± 3.75	-0.45 ± 3.94	NS
Years 1-4 (2,401)	-0.61 ± 4.17	-0.67 ± 4.38	NS
Years 1-5 (2,294)	-0.86 ± 4.66	-0.65 ± 4.88	NS
Years 1-6 (2,099)	-1.55 ± 4.91	-1.11 ± 5.10	NS

NS: not significant

5.2 MUSCLE STRENGTH AND QUALITY IN DIABETES

In cross-sectional analysis, older men with diabetes had lower muscle strength in the arm and knee than non-diabetic men. Muscle strength in older women with diabetes was not different from non-diabetic women. These results are completely against the general concept of the bigger the stronger. Our findings may imply that older adults with diabetes have double burden due to skeletal muscle weakness and a need to carry greater weight due to obesity. In fact, muscle quality (maximal strength per unit muscle mass) is consistently lower in both older men and women and in upper and lower extremities. Our findings strongly suggest that poor muscular function may act as a pathophysiological mechanism linking diabetes and physical limitations and disability. Unfortunately, this possibility has never been examined in the Health ABC cohort and other epidemiologic studies in older adults. [15-18] Future research should include measurements of skeletal muscle mass and strength to investigate potential association of muscle function and physical disability in older adults with diabetes.

Another novel finding of this study is a linear relationship between duration and severity of diabetes and poor muscle function. Muscle quality was the lowest in diabetic subjects with longer duration (> 6 years) and in those with poor glycemic control (A1c > 8%). It is consistent with previous findings in the Health ABC Study showing that diabetes with longer duration was associated with slow walking speed, poor standing balance, and lower summary physical performance score. [15] In addition, poor glycemic control among the diabetic population was associated with risk of subclinical functional limitation (OR 1.53 – 1.63) regardless of diabetes duration. [15] Poorer glycemic control in diabetes is associated with protein catabolism in skeletal muscle that may lead to loss of muscle mass and strength. Elevated inflammatory cytokines such as TNF-α and IL-6 may also be involved in this pathway. [19-20]

Peripheral neuropathy in diabetes is associated with decreased muscle strength in adults with type 2 diabetes as well as type 1 diabetes. [21-23] Not only the presence of neuropathy but also the severity of neuropathy assessed as combination of neuropathy symptom score, neurological disability score, vibration perception threshold, and the average of the rank scores of the motor nerve conduction velocity, compound muscle action potential, sensory nerve conduction velocity, and sensory nerve action potential, linearly correlated with isokinetic muscle strength at ankle and knee. [21, 23] Electrophysiologic study suggested incomplete reinnervation of nerve fibers following axonal loss in subjects with diabetes. [22] In our study, we have no measurements of nerve function at baseline thus we are unable to examine this potential pathway. Further research in the Health ABC Study may be needed to investigate the potential role of nerve function on muscle strength as we have assessments of nerve function at year 4 with strength measurements.

Whatever the mechanism, our longitudinal analysis clearly shows that older adults with diabetes lost about 50% greater amount of initial muscle strength than non-diabetic older adults in three years. Part of the rapid declines in muscle strength is attributable to greater loss of muscle mass. But, rapid declines in muscle strength is evident even after adjusting loss of muscle mass, suggesting there is a functional decline in muscle quality in older adults with diabetes. The result of longitudinal study confirms the cross-sectional association of diabetes and muscle weakness and highlights the importance of muscle quality.

5.3 UNIFYING HYPOTHESIS

From the cross-sectional and longitudinal study of skeletal muscle phenotypes in older adults, we have found significant deteriorations in muscular function in those with diabetes. Furthermore, we were able to explore some potential mechanisms of this association although it is incomplete (Figure 6).

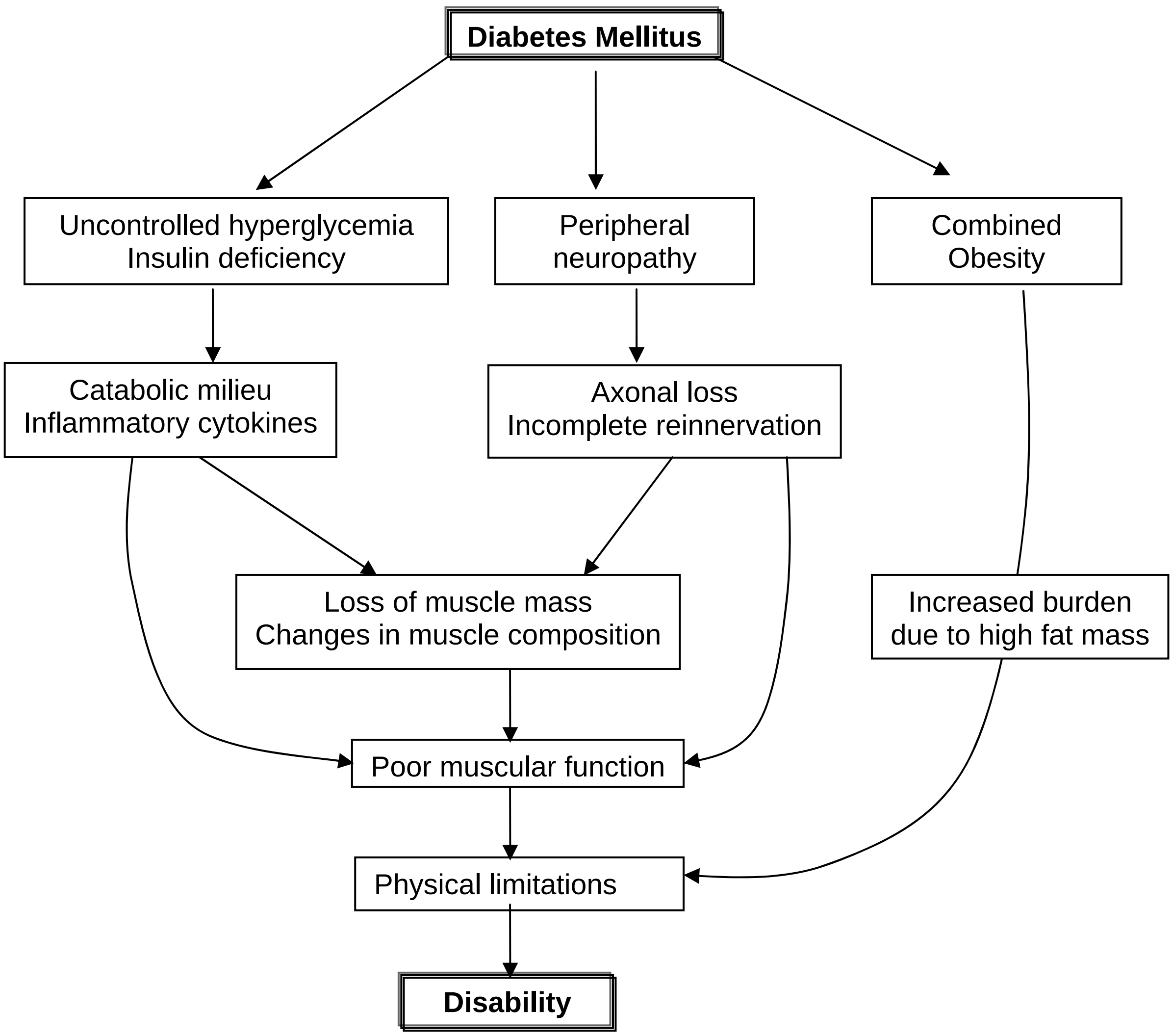

Figure 6. Unifying hypothesis explaining the association of diabetes and physical disability in older adults.

5.4 LIMITATIONS OF STUDY

Although the Health ABC Study seem to be an ideal cohort to examine the impact of diabetes on skeletal muscle mass and strength in older adults, we have several limitations which restrains in depth exploration of the association and pathways. First, our study population is physically well-functioning older adults at baseline excluding about one third of all age-eligible subjects who had difficulty walking one quarter of a mile or climbing 10 steps without rest. These selection criteria excluded many elderly people with poor function. Our diabetic participants may be a healthier selective population than usual older adults with diabetes. Perhaps this selection of healthier population may underestimate true declines in muscle mass and strength and our result is conservative in this respect. Second, there are many drop outs for the follow-up assessments of muscle mass and strength because of high mortality and morbidity in the study population. Part of drop-out is inevitable considering advanced age (average 73.5 years at baseline) of the population. Assessments of muscle mass require clinic visit of participants as we used DXA and CT. Furthermore, assessments of muscle strength require active involvement of participants especially for the knee strength tests. Many participants were excluded from knee strength test due to contraindications such as uncontrolled hypertension, recent stroke, brain aneurism, pain or history of joint replacement. However, as shown in the discussion of the second article, exclusion of participants for knee strength test biased the results to the null. Therefore, our findings are likely to be conservative. Third, we were unable to examine the influence of diabetic neuropathy as a potential pathway between diabetes and muscle function. But, the lack of nerve function assessment at baseline does not discount the significance of our findings because poor nerve function may be a mediator of association rather than confounding true association. Despite of these limitations, our study is novel as we clearly demonstrate the cross-sectional association of diabetes and poor muscle quality and it is confirmed by longitudinal analysis.

5.5 FUTURE RESEARCH

We have shown the impact of diabetes on skeletal muscle mass and strength in well defined cohort of older adults in the Health ABC Study. The next step will be "What is the clinical outcome of poor muscular function in older adults with diabetes?" Our findings suggest that poor muscular function in diabetes may have important role in the development of devastating outcomes like physical limitations and disability. Future study should identify the association of poor muscle function and clinical outcomes in older adults with diabetes. Secondly, biological mechanisms involved in the association of diabetes and poor muscle function need to be investigated more thoroughly. We have suggested some potential mechanisms such as uncontrolled hyperglycemia, inflammatory cytokines, and diabetic neuropathy. It seems very important to explore the association with nerve function because muscle function is under the direct control of nerve function and muscle and nerve are connected as a neuromuscular system rather than two separate systems. We hope this will be examined in the Health ABC Study by using year 4 data as a baseline. Thirdly, we have no clear answer why older adults with undiagnosed diabetes show greater declines in skeletal muscle mass. Many issues including intention to lose weight can be raised in this association. Modification of this association by treatment effects in known diabetes should also be explored.

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6. APPLICATION TO PUBLIC HEALTH

The present study is the first epidemiologic study to assess skeletal muscle mass and strength in subjects with and without diabetes in apparently healthy, community dwelling older adults. Our study population includes white and black older men and women with type 2 diabetes in various clinical stages. The prevalence of diabetes is increasing especially in older adults and about one third of diabetes is remained undiagnosed. [1-3] If older adults with undiagnosed diabetes were left untreated they would be at high risk for weight loss, particularly loss of lean mass. It is important because accelerated loss of lean mass in older adults with diabetes might be related to muscle strength loss, functional limitations, and physical disability. [4-7]

In our aging society, the diabetes epidemic continues to garner headlines, with the emergence of obesity epidemic. The prevalence of elderly diabetes is rising and the impact of elderly diabetes is likely to be dramatic in the next decade. [8] It is anticipated that elderly diabetes combined with obesity will give rise to huge public health problem. It is already evident that over 1.2 million (or approximately one-fourth) of older American diabetic adults either cannot walk one quarter of a mile, climb 10 stairs, or do housework. Over 2.5 million (or approximately one-half) have some difficulty doing these tasks. [4] Our results suggest that loss of muscle mass and strength may contribute to the functional disability in older adults with diabetes because adequate muscle mass and strength is essential for physical functioning.

We are urgently in need to develop strategies to slow or prevent rapid declines in muscle mass and function in this high risk population of older adults with diabetes. Every potential ways such as strict glucose control and resistive training exercise programs should be examined thoroughly. [9] Now, it is time to develop preventive strategy to reduce anticipated devastating consequences in the high risk population of older adult with diabetes.

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