

Aging, physical activity, and diabetic complications related to loss of muscle strength in patients with type 2 diabetes

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ABSTRACT. Patients with type 2 diabetes may have motor dysfunctions such as loss of muscle strength. Compared with non-diabetic subjects, patients with diabetes show decreased lower extremity muscle strength. The aim of this review was to describe the influence of factors associated with loss of muscle strength in patients with type 2 diabetes. Aging promotes an accelerated loss of muscle strength in patients with diabetes. Physical inactivity may cause a decline in muscle strength in patients with diabetes. Gradual loss of muscle strength is related to the presence and severity of diabetic neuropathy. Diabetic nephropathy may be a factor contributing to loss of muscle strength, because decrease in skeletal muscle mass is a hallmark of end-stage renal disease. Resistance exercise is an essential component of diabetes treatment regimens and also plays a role in the prevention and management of sarcopenia. Intensive physical therapy intervention should be provided to patients with diabetes having decreased muscle strength.

Key words: type 2 diabetes, muscle strength, aging, physical activity, diabetic complications

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The prevalence of type 2 diabetes is increasing worldwide¹. According to a previous study, diabetic patients may present with motor skills deficits²; additionally, an early decline in physical function with age has been associated with type 2 diabetes³. These facts represent a serious problem, as the number of people aged >65 years is expected to continue to rise in developed countries such as Japan, Germany, and Italy⁴. The discovery of more effective measures to prevent movement disorders⁵ is essential for patients with diabetes in a country with an increasingly aging population. In the elderly, mobility-related fatigue is associated with slower walking speed, and current evidence suggests that muscle strength is one of the underlying factors ex-

plaining this association⁶. Furthermore, in elderly patients, leg muscle strength has been shown to be associated with balance and mobility skills⁷. Therefore, it is important that healthcare professionals and medical teams pay attention to the loss of muscle strength in patients with diabetes.

In the present review article, we describe the influence of factors associated with loss of muscle strength in patients with type 2 diabetes.

Muscle Strength in Diabetes

Insulin resistance, hyperglycemia, muscle fat infiltration, peripheral neuropathies, and oxidative stress are hypothesized as the fundamental biological mechanisms leading to impairments in muscle strength in people with diabetes^{8,9}. Our previous study suggested that knee extension force (KEF) is independently associated with insulin resistance in patients with type 2 diabetes¹⁰ (Table 1). These factors are likely to affect muscle strength in patients with type 2 diabetes.

We examined reference values for KEF (kgf; absolute value) and %KEF (%; body weight ratio) based on data

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Table 1-1. Outline of references about related factors of loss of muscle strength in diabetic patients in present review article

Related factors	References	Materials/Trial title	Methods/Statistical Analysis	Results
Insulin resistance	10) Nomura T, et al. J Endocr J. 2007	40 patients (20 men) with type 2 diabetes (53.3 ± 12.7 years)	Correlation between different parameters were determined using Pearson product-moment correlation coefficients. Multiple regression analyses were conducted using a stepwise method. Age, HOMA-IR, and regular exercise habits, etc. were incorporated as independent variables for analysis of %KEF.	In simple linear regression analyses, the knee extension force normalized for body weight (%KEF) significantly correlated with HOMA-IR in both male ($r = -0.462$) and female patients ($r = -0.510$). The stepwise regression analysis showed that %KEF was an independent determinant of HOMA-IR ($\beta = -0.331$, $F = 5.400$), as were BMI ($\beta = 0.409$, $F = 8.260$).
	13) Leenders M, et al. J Am Med Dir Assoc. 2013	60 men with type 2 diabetes (71 ± 1 years) and 32 age-matched normoglycemic controls (70 ± 1 years)	Muscle mass (DEXA and muscle biopsies), strength (1-repetition maximum), functional capacity (sit-to-stand test and handgrip strength), and reaction time performance (computer task) were compared between the 2 groups. Data were analyzed using ANCOVA to adjust for several potential confounders.	Leg lean mass and appendicular skeletal muscle mass were significantly lower in older men with type 2 diabetes (19.1 ± 0.3 and 25.9 ± 0.4 kg, respectively) compared with controls (19.7 ± 0.3 and 26.7 ± 0.5 kg, respectively). Leg extension strength was significantly lower in the group with type 2 diabetes (84 ± 2 vs 91 ± 2 kg, respectively). Muscle fiber size and reaction time performance did not differ between groups.
Accelerated aging	14) Park SW, et al. Diabetes. 2006	485 with diabetes and 2,133 without diabetes, aged 70-79 years Health ABC study	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 DEXA. To test the effects of duration and severity of diabetes on muscle strength and quality, ANOVA tests for trend were used. When overall differences were significant with ANOVA, post hoc comparisons were performed with Bonferroni adjustment.	Older men and women with diabetes had higher weight, BMI, total body fat, and total body lean mass than nondiabetic counterparts. Those with diabetes reported less alcohol use and less physical activity. 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 years) and poor glycemic control (HbA1c >8.0%) were associated with even poorer muscle quality.
	15) Park SW, et al. Diabetes Care. 2007	Among the 1,840 older adults, 305 (16.6%) had type 2 diabetes at baseline, aged 70-79 years Health ABC study	Longitudinal changes of muscle strength and quality were calculated in both absolute terms and relative terms (percent change from baseline). Differences between older adults with and without diabetes were assessed by general linear models controlling for sex, race, age, and clinic site.	Both diabetic and nondiabetic older adults lost significant amounts of initial muscle strength in 3 years. However, older adults with type 2 diabetes lost their KEF more rapidly than those without diabetes. Older adults with type 2 diabetes also lost greater amounts of leg lean mass than those without diabetes. Muscle quality significantly declined more rapidly in older adults with type 2 diabetes.

Table 1-2. Outline of references about related factors of loss of muscle strength in diabetic patients in present review article

Related factors	References	Materials/Trial title	Methods/Statistical Analysis	Results
Physical inactivity	21) Lee IM, et al. Lancet. 2012	This study contacted several large cohort studies throughout the world using input from the Lancet Physical Activity Series Working Group. This study applied the average adjustment factor to the prevalence of physical inactivity, by country, to estimate the prevalence of inactivity in cases of type 2 diabetes, etc., and death from any cause.		Worldwide, this study estimate that physical inactivity causes 6% of the burden of disease from 7% (3.9-9.6) of type 2 diabetes. For the association of type 2 diabetes incidence with physical activity, reported a pooled RR of 0.83 (95% CI 0.76-0.90)
	23) Nomura T, et al. J Diabetes Investig. 2018	1,442 patients with type 2 diabetes, aged 30-87 years MUSCLE-std study	Regular exercise behavior as the response variable was defined as 1 (action stage or earlier [<6 months]) or 2 (maintenance stage or later [≥ 6 months]). Using logistic regression analysis, the relationship of KEF in combination with regular exercise was analyzed by sex. Continuous explanatory variables included KEF, age, body mass index, etc.	In sex-specific univariate analysis, KEF was significantly higher in patients with regular exercise than in patients without regular exercise. Age, but not exercise behavior, was significantly different between KEF quartiles. In the multivariate analyses using age and other parameters as covariates, KEF was a significant explanatory variable of regular exercise in both men and women, suggesting that muscle strength may influence regular exercise behavior.
	26) Andersen H, et al. Diabetes. 2004	36 type 2 diabetic patients and in 36 control subjects	The degree of neuropathy was determined by clinical scores and nerve conduction studies, etc. All results were summed to obtain a NRSS. The correlations between muscle strength and NRSS and the various biochemical findings, linear regression analysis was applied.	Diabetic patients had a 17% and 14% significantly reduction of strength of ankle flexors and ankle extensors, respectively. At the knee, strength of extensors and flexors was reduced by 7% (NS) and 14% ($P<0.05$), respectively. The NRSS was significantly related to the strength at the ankle ($r = -0.45$) and knee ($r = -0.42$).
Diabetic neuropathy	25) Nomura T, et al. J Diabetes Investig. 2018	1,442 patients with type 2 diabetes, aged 30-87 years MUSCLE-std study	KEF was compared according to the presence or absence of DPN. Furthermore, the effect of DPN on KEF with other diabetic complications, diabetes status and habitual behavior as explanatory variables was analyzed using multiple regression analysis.	Among both men and women patients aged 50-69 years and 70-87 years, patients with DPN showed significantly diminished KEF (11.0-12.9%, 11.9-16.6%, respectively) compared with those without DPN. In women aged 50-69 years and 70-87 years, and in men aged 50-69 years, DPN was a significant explanatory variable for KEF in all multiple regression analysis models.
	31) Sato E, et al. Sci Rep. 2016	Mouse model of CKD	Imaging mass spectrometry revealed indoxyl sulfate accumulated in muscle tissue of a mouse model of CKD. Comprehensive metabolomics revealed that indoxyl sulfate induces metabolic alterations, such as upregulation of glycolysis, including pentose phosphate pathway acceleration as antioxidative stress response, via nuclear factor (erythroid-2-related factor) -2. The altered metabolic flow to excess antioxidative response resulted in downregulation of TCA cycle and its effected mitochondrial dysfunction and ATP shortage in muscle cells. In clinical research, a significant inverse association between plasma indoxyl sulfate and skeletal muscle mass in CKD patients is observed.	

Abbreviations: ANCOVA, analysis of covariance; ANOVA, analysis of variance; CI, confidence interval; CKD, chronic kidney disease; DEXA, dual-energy X-ray absorptiometry; DPN, diabetic poly neuropathy; HOMA-IR, homeostatic model assessment insulin resistance; KEF, knee extension force; NRSS, neuropathy rank-sum score; RR, relative risk.

from type 2 diabetic patients with a wide age range who did not have diabetic polyneuropathy (DPN). In type 2 diabetic patients without apparent DPN compared with non-diabetic subjects, KEF and %KEF may be reduced by approximately 10% and 20%, respectively¹¹.

Aging Muscle and Relation to Diabetes

There is an interrelationship between muscle strength and aging¹². A natural decrease in muscle strength occurs with increasing age; however, patients with type 2 diabetes show greater decline in muscle strength with age^{13,14}. Furthermore, accelerated loss of muscle strength is observed in elderly patients with type 2 diabetes¹⁵. Loss of muscle strength is a predictor of functional limitations¹⁶; muscle strength is also the single best measure of age-related muscle change and is associated with physical disability in instrumental activities of daily living. Moreover, diabetes-related loss of muscle strength predisposes this population to a higher fall risk^{17,18}.

Regular Physical Activity and Physical Function in Patients with Diabetes

Physical activity (PA) has been associated with better mobility in the elderly^{19,20}. The associations between physical inactivity and type 2 diabetes is well known²¹. The relationship between PA and physical function (PF) is bidirectional, with PF more consistently predicting declines of PA²². In a sex-specific univariate analysis, KEF was significantly higher in patients who regularly exercised than in patients who did not regularly exercise²³. Moreover, in the multivariate analyses using age and other parameters as covariates, KEF was found to be a significant explanatory variable of regular exercise in both men and women, suggesting that muscle strength could influence regular exercise behavior.

Loss of Muscle Strength Related to Diabetic Neuropathy

Demyelination and axonal degeneration are established hallmarks of diabetic neuropathy (DN) pathophysiology²⁴. One of the common forms of DN is DPN, which is further classified into a sensory nerve disorder, motor nerve disorder, or autonomic nerve disorder. DPN is a diabetic complication to most clinically combine to patients with diabetes. In our previous study, the incidence of DPN was 37.7% in 1,442 patients with type 2 diabetes²⁵.

The gradual loss of muscle strength in type 2 diabetes is related to the presence and severity of DPN²⁶. No population-based studies on this topic have been carried out, and the characteristics of diminished muscle strength according to sex or age group have not been determined. In

our previous study, comparisons of KEF according to sex and age group showed neither men nor women aged 30-49 years had a significant difference in KEF based on their DPN status. On the other hand, both men and women participants aged 50-69 years and 70-87 years with DPN showed a significantly diminished KEF by 10.9-16.5% compared with those without DPN²⁵. These results show that DPN might accelerate lower extremity muscle strength decline in middle-aged and elderly type 2 patients with diabetes.

Loss of Muscle Strength Related to Diabetic Nephropathy

Diabetes affects the small blood vessels in the glomerulus, a key structure in the kidney composed of capillary blood vessels. Diabetic nephropathy represents a leading cause of ongoing dialysis²⁷, accounting for 38.4% of dialysis usage in Japan in 2015²⁸.

Chronic kidney disease (CKD) as a clinical entity is a relatively new concept, with diabetes and high blood pressure being listed as the two main causes²⁹. It is known that elderly patients with CKD show decreased physical function, quality of life, and mental health³⁰. Sato et al. reported that the causative pathological mechanism of uremic sarcopenia is metabolic alterations by uremic toxin indoxyl sulfate in a mouse model of CKD³¹. Moreover, a significant inverse association between plasma indoxyl sulfate and skeletal muscle mass in CKD patients was observed in clinical research³¹. Previous reports indicate that indoxyl sulfate may be a pathogenic factor for sarcopenia in CKD. These facts show that skeletal muscle dysfunction and poor exercise tolerance are hallmarks of end-stage renal disease.

Exercise for Loss of Muscle Strength in Patients with Diabetes

Exercise therapy is well-established as a fundamental treatment for patients with type 2 diabetes³². Two possible exercise interventions for type 2 diabetes are aerobic and resistance exercise; more specifically, moderate- or high-intensity resistance exercise has been reported as a potentially effective means to improve muscle strength and physical function³³. Resistance exercise is a crucial means to treat diabetes-related loss of muscle strength and prevent and manage sarcopenia. However, strict blood pressure control is required according to the severity of the diabetic complications such as diabetic retinopathy and diabetic nephropathy³⁴. High-intensity exercise therapy raises blood pressure; therefore, it is essential to make the appropriate individual adjustments.

Conclusion

This review discussed factors related to the loss of muscle strength in patients with type 2 diabetes. There is an acceleration in the typical age-related decrease in muscle strength in elderly patients with diabetes. Current literature shows that the presence of DPN is the main factor contributing to loss of muscle strength in patients with type 2 diabetes; this fact is especially clear in middle-aged and elderly patients. Skeletal muscle dysfunction and poor exercise tolerance are hallmarks of end-stage renal disease. Intensive physical therapy intervention should be provided to diabetic patients with a loss of muscle strength³⁵.

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