

Sarcopenia, Frailty, and Diabetes in Older Adults

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Populations are aging and the prevalence of diabetes mellitus is increasing tremendously. The number of older people with diabetes is increasing unexpectedly. Aging and diabetes are both risk factors for functional disability. Thus, increasing numbers of frail or disabled older patients with diabetes will increase both direct and indirect health-related costs. Diabetes has been reported as an important risk factor of developing physical disability in older adults. Older people with diabetes have lower muscle mass and weaker muscle strength. In addition, muscle quality is poorer in diabetic patients. Sarcopenia and frailty have a common soil and may share a similar pathway for multiple pathologic processes in older people. Sarcopenia is thought to be an intermediate step in the development of frailty in patients with diabetes. Thus, early detection of sarcopenia and frailty in older adults with diabetes should be routine clinical practice to prevent frailty or to intervene earlier in frail patients.

Keywords: Diabetes; Disability; Frailty; Sarcopenia

The Sulwon Award for Scientific Achievement is the Korean Diabetes Association's highest scientific award and honors an individual who has excellently contributed to the progress in the field of diabetes and metabolism. Sulwon Award is named after an emeritus professor Eung Jin Kim, who founded Korean Diabetes Association. Prof. Hak Chul Jang received the seventh Sulwon Award at 2015 International Conference on Diabetes and Metabolism, October 15-17, 2015 at Jeju Island, Korea.


INTRODUCTION

Increased life expectancy and declining fertility has brought dramatic shifts in the age structure worldwide [1]. Large populations are aging and this has become a global social and health burden. A progressive decline in muscle mass and strength, termed sarcopenia, develops as a consequence of aging [2]. The prevalence of sarcopenia reported varies widely depending on the definition and methods of assessment; it ranges from 8% to 40% of people aged over 60 years [3,4]. Sarcopenia results in frailty, loss of independence, physical dis-

ability, and increased mortality in older adults [5,6].

Diabetes mellitus is a prevalent chronic disease, especially in older adults, that is associated with microvascular and cardiovascular complications [7]. More than 25% of Korean people over age 60 years have diabetes mellitus [8,9]. Diabetes has been associated with an increased risk of developing physical disability in older adults [10,11]. Chronic conditions such as visual disturbances, diabetic complications, comorbidities, and depression are associated with physical disability in patients with diabetes; however, these account for only some of the impairments [12]. It was also reported that men and women with diabetes diagnosed at age 60 have estimated reductions in life expectancy of 7.3 and 9.5 years and good quality of life of 11.1 and 13.8 years, respectively [13].

Physical and cognitive function becomes of great importance in the care of older people with diabetes. A key strategy is to prevent the functional decline instead of attempting to recover lost function. In this review, the relationship between sarcopenia, frailty, and physical disability in older adults with diabetes will be discussed.

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SARCOPENIA AND DIABETES

A progressive decrease in muscle mass, especially of the lower extremities and an increase in fat mass, especially of visceral and intermuscular fat are common body compositional changes associated with aging [14,15]. After 30 years of age, muscle mass is reported to decline at an annual rate of approximately 1% to 2%, and that accelerates to as much as 1.5% to 3% per year after age 60 years, becoming ever faster after age 75 years (Fig. 1) [4,15].

Baumgartner et al. [16] first proposed that the appendicular skeletal muscle mass (ASM) divided by height squared (ASM/ht^2) was as a representative muscle index. Clinically, sarcopenia was defined as relative ASM index less than 2 standard deviations below the mean values of healthy young adults or the lowest quintile of study populations [16,17]. However, recent studies have indicated that decline in muscle

strength may be more important in the health outcomes related to sarcopenia [18]. Based on this, the European Working Group for Sarcopenia in Older People proposed reduced muscle mass with either muscle weakness or poor physical performance as the criteria for sarcopenia [2]. These criteria demonstrated better associations with various outcomes compared with the definitions driven only by muscle mass [19,20].

Meanwhile, the Foundation for the National Institutes of Health (FNIH) Sarcopenia Project has suggested a new criteria for sarcopenia categorized by muscle mass, muscle strength, and physical performance [21]. They proposed a new muscle mass index of ASM divided by body mass index. However, data about the clinical implications of the new FNIH criteria remain sparse.

Muscles play various important roles in the human body; thus, loss of muscle mass and strength can cause a diverse range of functional disability and metabolic derangements in older adults. Sarcopenia has been closely related to many clinical consequences, including functional disability, metabolic impairment, increased cardiovascular risk, and mortality, in the older Korean adults [6,22-25].

However, studies of sarcopenia in older adults with diabetes are few. The Health, Aging, and Body Composition (Health ABC) Study showed that older adults with type 2 diabetes lost their knee extensor strength more rapidly than nondiabetic subjects did [26]. In that study, diabetic patients had greater declines in muscle mass and leg muscle strength, and muscle quality was poorer in diabetic patients over 3 years. In addition, thigh muscle cross-sectional area also declined twice as fast in older women with diabetes than in nondiabetic subjects over 6 years [27]. Further, the Hertfordshire study demonstrated that older men newly diagnosed with diabetes have significantly weaker muscle strength and higher odds of impaired physical function than those without diabetes do [28]. Leenders et al. [29] also showed that leg lean mass and appendicular skeletal mass were significantly lower in older men with diabetes. Further, leg-extension strength in patients with diabetes was weaker than in nondiabetic subjects, and functional performance was impaired in older diabetic men. Other studies also have demonstrated that leg muscle strength and gait speed is reduced in older peoples with diabetes [30,31]

Kim et al. [32] reported that in Korean men and women aged ≥ 65 years, ASM was lower in diabetic patients compared with nondiabetic subjects but relative muscle index ($\text{ASM}/$

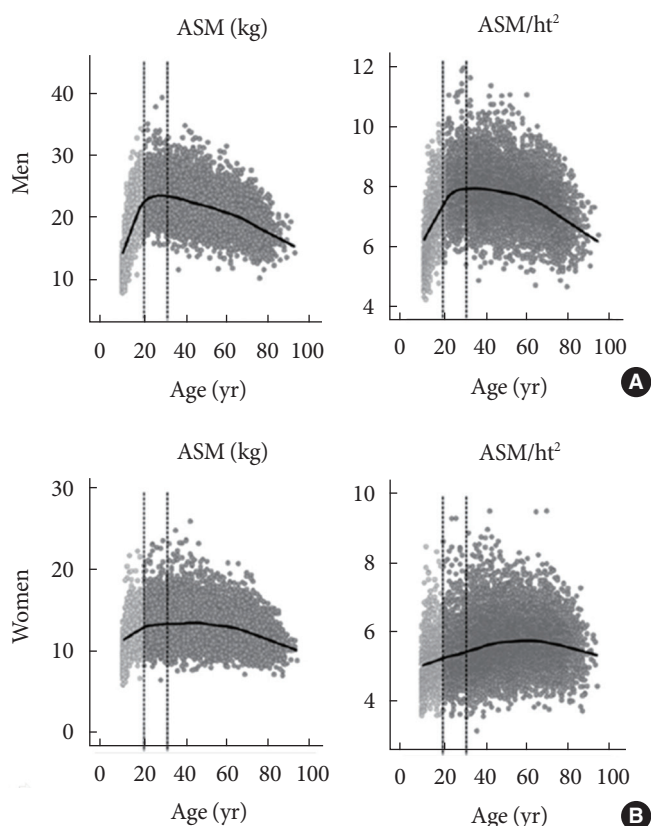


Fig. 1. Changes of appendicular skeletal muscle mass (ASM), and ASM indices according to age trends in Korean (A) men and (B) women using data from Korea National Health and Nutrition Examination Study 2008 to 2010. ht^2 , height squared (m). Modified from Kim et al. [4].

height²) was lower only in older men with diabetes. The Korean Sarcopenic Obesity Study showed that sarcopenia (skeletal muscle mass/weight $\times 100 < 2$ SD below the mean of the young reference) was present in 15.7% in subjects with diabetes and 6.9% in the control subjects [33]. Yoon et al. [34] demonstrated that muscle mass and strength in older diabetic patients were not different compared with nondiabetic subjects, but muscle quality was poorer and physical performance was impaired in diabetic subjects with poor glycemic control.

PATHOPHYSIOLOGY OF SARCOPENIA IN DIABETES

Multiple factors are associated with decreased muscle mass and/or strength in older adults [2,17]. The major causes or mechanisms related to sarcopenia include inadequate nutrition, physical inactivity or disuse, age-related hormonal changes including sex hormone and growth hormone, loss of motor neurons, atherosclerosis, obesity, insulin resistance, and inflammatory cytokines (Table 1).

Additionally, diabetes mellitus will accelerate the reduction of muscle mass and strength because hyperglycemia, diabetic complications, obesity, insulin resistance, inflammatory cytokines, and endocrine changes associated with diabetes have adverse effects on muscle [35].

The mechanism of hyperglycemia that is associated with accelerated reduction of muscle mass and strength is still unclear. Weight loss associated with hyperglycemia may result in the loss of muscle mass and strength [36]. It is also reported

that amino acid metabolism decreases in type 2 diabetes [37]. Insulin resistance inhibits the mammalian target of the rapamycin pathway that leads to protein synthesis and decreases protein degradation [38]. Insulin resistance also increases activation of the ubiquitin-proteasome pathway, resulting in degradation of muscle protein [37].

Chronic hyperglycemia increases advanced glycation end products (AGEs). AGEs accumulate in skeletal muscle and cartilage and increase the stiffness in patients with diabetes. It was reported that elevated AGEs were associated with poor grip strength in older women with moderate to severe disability and slow walking speed in older community-dwelling adults [39,40]. Higher skin autofluorescence, a noninvasive measurement of tissue AGEs, has been associated with lower grip strength and leg-extension power in Japanese men [41].

Another major cause of sarcopenia in diabetes is a decrease in motor neurons [42]. Diabetic neuropathy is a common complication of diabetes, especially in older adults, and it leads to muscle wasting and weakness of distal skeletal muscles [31]. Electrophysiological studies have shown that muscle strength of the ankle and knee extensors in patients with diabetes are correlated with fiber density and the amplitude of the macro motor unit potential [43], suggesting the loss of muscle strength because of incomplete reinnervation after axonal loss. A longitudinal follow-up study for diabetic polyneuropathy has shown that 8.3% of the patients had electrophysiological abnormalities at baseline; 16.7% had such abnormalities at 5 years; and 41.9% at 10 years [44]. Interestingly, diabetic patients with peripheral neuropathy had higher calf intermuscular adipose tissue volume, and higher adipose tissue volume was associated with poor muscle strength and physical function [45].

Diabetes is associated with an increase in inflammatory cytokines. It has been reported that systemic inflammatory cytokines such as tumor necrosis factor and interleukin 6 have detrimental effects on muscle mass, strength, and physical performance in older adults [46,47].

Testosterone increases satellite cell numbers and protein synthesis in muscle [48]. Serum testosterone levels decline gradually and progressively with aging in men. The men with diabetes and/or obesity have lower serum testosterone levels. Therefore, testosterone deficiency is another cause of sarcopenia in patients with diabetes.

Table 1. Major causes or mechanisms of sarcopenia in older adults

Primary	Age related: sex hormones, muscle apoptosis, mitochondrial dysfunction
Secondary	Activity related: physical inactivity, disuse, deconditioning, zero gravity
	Nutrition related: inadequate dietary intake, malabsorption, gastrointestinal disorders or medications that cause anorexia
	Endocrine disorder related: obesity, insulin resistance, inflammatory cytokine, steroid treatment, abnormal thyroid function
	Neurodegenerative disorder related: stroke, parkinsonism, diabetic neuropathy
	Chronic disease related: malignancy, advanced organ failure

FRAILITY AND DIABETES

Frailty is a common geriatric syndrome in older adults that carries an increased risk for poor health outcomes including falls, incident disability, hospitalization, and mortality because of decreased physical reserves [49]. Although agreement between a theoretical concept and an operational definition is lacking [50], Fried et al. [49] defined a clinical phenotype of frailty, which was identified by the presence of three or more of the five components (Table 2). An individual with one or two of the five components was considered prefrail. Frailty seems to be a dynamic process and also potentially reversible. Therefore, early detection of frailty and prevention or early interventions should be key issues in the care of older adults.

Fried et al. [51] also proposed the cycle of frailty, in which sarcopenia was one of the main potential causes of frailty. Actually, sarcopenia and frailty have a commonality and may share the similar pathway for multiple pathologic processes in older people. Thus, sarcopenia may be an intermediate step in the development of frailty in patients with diabetes.

Several studies have shown that diabetic patients aged 65 years or older were more likely to be frail than nondiabetic older adults were [52-54]. These studies also reported that frail patients with diabetes had a higher mortality than non-frail patients, and the presence of frailty was an independent risk factor for mortality. The German ESTHER (*Epidemiologische Studie zu Chancen der Verhütung, Früherkennung und optimierten Therapie chronischer Erkrankungen in der älteren Bevölkerung*) study and the Whitehall II Prospective Study demonstrated that the prevalence of frailty was 3- to 5-fold higher in patients with diabetes older than 65 years than that

seen in the general population [55,56].

MANAGEMENT OF FRAILITY IN DIABETES

Morley et al. [35] suggested that the management of frailty in patients with diabetes initially should focus on the prevention of sarcopenia. Several consensus reports recommended the measurement of gait speed as a screening method on clinical practice [2,17]. Until now, no pharmacologic agent to prevent or treat sarcopenia has proven to be as efficacious as exercise (mainly resistance training) in combination with nutritional intervention (adequate protein and energy intake) [57]. This approach is currently the key strategy for the management of sarcopenia and frailty.

Larger muscles in the body move in a rhythmic manner for a prolonged period during aerobic exercise, whereas resistance exercise involves muscles working hard against an applied force or weight such as in weight lifting. Both aerobic and resistance exercise training have been shown to prevent the decline in muscle mass and strength with age [58]. Although aerobic exercise is less likely to contribute to muscle hypertrophy, it has been linked to improvements in cardiovascular fitness and endurance capacity. Aerobic exercise can also reduce body fat including intra- and intermuscular fat, which in turn improves the functional role of muscle relative to body weight [59,60]. In contrast, resistance exercise training appears to have a larger effect on augmenting muscle mass and strength, and it attenuates the development of sarcopenia [61,62]. Improvements in muscle strength can be achieved with as little as one resistance exercise training session per week [63].

Many older people do not consume sufficient amounts of dietary intake and protein, which leads to a reduction in lean body mass and increased functional disability [64]. The current recommended dietary allowance (RDA) of dietary protein is 0.8 g/kg/day, but 40% of people aged over 70 years did not meet this RDA [65]. Older women taking a low protein diet below the RDA had a significant decline in muscle mass and strength [66]. Further, older people who took the protein of RDA had a negative nitrogen balance and might require a higher protein content than the RDA to maintain their skeletal muscle [67]. Although older adults who exercise may have additional protein requirements, studies investigating whether nutritional supplementation in combination with resistance exercise can augment muscle strength and mass have yielded

Table 2. Clinical phenotype of frailty proposed by Fried et al.

Weight loss	Unintentional loss of ≥ 4.5 kg in the past year
Weakness	Hand-grip strength in the lowest 20% quintile adjusted for sex and body mass index
Exhaustion	Poor endurance and energy, self-reported from the Center for Epidemiologic Studies Depression Scale
Slowness	Walking speed under the lowest quintile adjusted for sex and height
Low physical activity level	Lowest quintile of kilocalories of physical activity during the past week, measured by the Minnesota Leisure Activity Scale

Modified from Fried et al., with permission from Oxford University Press [49].

inconsistent results [68]. Nutritional supplementation may result in an overall decrease in voluntary food intake and adherence to the supplements can be a problem [69].

Additionally, three treatable causes should be managed for the treatment of frailty [35]: (1) treatable causes of fatigue: vitamin B12 deficiency, adrenal inefficiency, hypothyroidism, anemia, sleep apnea, hypotension, syncope, and depression; (2) polypharmacy: anticholinergic medication, overtreatment of blood pressure, hypoglycemia; (3) and unintentional weight loss: depression, medications, dysphagia, dental problems, and nosocomial infections.

CONCLUSIONS

As larger populations are now aging, there is a tremendous increase of older adults with diabetes. Aging and diabetes are both risk factors for functional impairment. A recent systematic review article showed that diabetes is associated with a strong increase in the risk of physical disability in older adults [11]. This will increase both direct and indirect health-related costs. I believe that early detection of sarcopenia and frailty in older adults with diabetes should be routine clinical practice to facilitate early multimodal interventions.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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