

# Sarcopenia and diabetes: Hyperglycemia is a risk factor for age-associated muscle mass and functional reduction

Skeletal muscle maintains our posture and produces body movement. Muscle is essential to make all movements required in daily life. Skeletal muscle has several other roles. It is a major target of insulin. Insulin receptors in the muscle play a major role in glucose regulation, and muscle is a major site of glucose disposal. Muscle is also a fuel source under certain conditions, such as starvation, and provides amino acids for gluconeogenesis in the liver. Recent studies have shown that skeletal muscle secretes several factors, so-called myokines, which are associated with maintaining healthy conditions.

From the age of approximately 30 years, human muscle mass and function (power) progressively decrease. Gait speed and hand grip decrease with age. The age-associated decrease of muscle mass and function is called sarcopenia. Sarcopenia has been reported to be associated with several unhealthy age-related conditions including mobility disorders, falls and fractures, impaired activities of daily living, disabilities, loss of independence and increased risk of death<sup>1</sup>. Sarcopenia and central obesity are both age-related body compositional changes, and are often combined in older individuals. Central obesity with sarcopenia is known as sarcopenia obesity. It is reportedly a higher risk factor for metabolic syndrome and atherosclerosis than simple obesity.

Insulin resistance is involved in one of several underlying mechanisms of sarcopenia induction. Insulin is a catabolic hormone, which stimulates protein syn-

thesis including the synthesis of muscle. The process of protein degradation and synthesis constantly repeats in skeletal muscle. Defects in insulin signaling can lead to reduced muscle synthesis. Chronic inflammation and mitochondrial dysfunction are also considered to be involved. Age-related sex hormone reduction or other hormonal changes including changes in growth hormone, insulin-like growth factor-1 and corticosteroids have been reported to be associated with sarcopenia. The loss of neuromuscular integrity might also be involved in sarcopenia. In older individuals, muscle disuse because of physical inactivity and malnutrition are also associated with sarcopenia. In turn, the reduced muscle mass due to sarcopenia results in a diminished target of insulin, and can alter insulin sensitivity and glucose regulation.

Sarcopenia is also associated with frailty. Frailty has been defined as a pre-disability condition, and the validity of the framework of the frailty phenotype, which was developed by Fried *et al.*<sup>2</sup>, has been well established. This phenotype contains five components: low grip strength, exhaustion, physical inactivity, slow walking speed and weight loss. Sarcopenia is a major component of frailty, and sarcopenia and frailty often overlap. Many older subjects who exhibit frailty have sarcopenia, and many people with sarcopenia exhibit frailty syndrome. Frailty is associated with a number of adverse health outcomes, such as disability, falls, hospitalization, institutionalization and mortality. Frailty is also associated not only with physical function, but also mental function. There is evidence that frailty increases the risks of dementia and depression, which are also

closely associated with diabetes mellitus. Frailty, however, is a reversible condition. Frequent transitions among frail, prefrail and non-frail conditions have been reported. Therefore, frailty is a good target for the prevention of disability states. Thus far, interventions with nutrition including amino acids and exercise in individuals with sarcopenia/frailty have been carried out; however, the effects of these interventions are relatively limited, and more efficacious measures are warranted.

It has been well established that type 2 diabetes mellitus is a risk factor for functional disability and for mobility limitations. Several reports have shown that type 2 diabetes mellitus is associated with sarcopenia and frailty. In a study carried out in Korea, patients with diabetes had a threefold higher risk of sarcopenia (odds ratio 3.06, 95% confidence interval 1.42–6.62) than subjects without diabetes after adjusting for several confounding factors<sup>3</sup>. Sarcopenia is likely to be involved in the underlying mechanisms of increased functional disability and mobility limitations in older diabetes mellitus patients.

Although ample evidence has suggested that older diabetes mellitus patients have increased risks of sarcopenia and frailty<sup>4</sup>, so far the underlying mechanism of the association between sarcopenia/frailty and type 2 diabetes mellitus has not been clarified. Insulin resistance is common in older diabetes mellitus patients. Reduced insulin signaling leads to decreased protein synthesis and increased protein degradation, which can ultimately lead to reduced muscle mass. Chronic inflammation, oxidative damage, and mitochondria dysfunction have also been suggested to be associ-

\*Corresponding author. Hiroyuki Umegaki

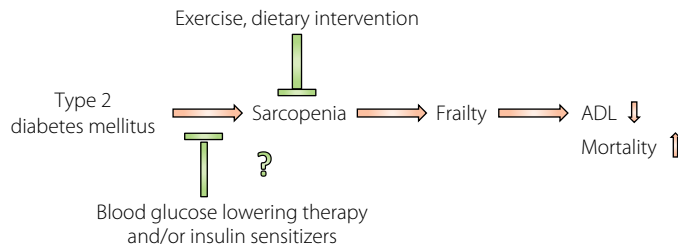
Tel: +81-52-744-2364

Fax: +81-52-744-2371

E-mail address: Umegaki@med.nagoya-u.ac.jp

Received 6 April 2015; revised 12 April 2015;

accepted 13 April 2015



**Figure 1** | Exercise and/or dietary intervention prevent the progress of sarcopenia. Blood glucose-lowering therapy might also prevent the progression. ADL, activities of daily living.

ated with both diabetes mellitus and sarcopenia. Some reports have suggested that diabetic neuropathy might be involved in the mechanism of sarcopenia in older diabetic patients. The relationship between hyperglycemia per se and sarcopenia, however, has been relatively underinvestigated.

Kalyani *et al.*<sup>5</sup> recently reported that using Baltimore Longitudinal Study of Aging data, hyperglycemia measured by glycated hemoglobin (HbA1c) is associated with the lower muscle strength that occurs with aging. That study included 984 participants in the Baltimore Longitudinal Study of Aging and divided them into quartiles according to their HbA1c levels (<5.5%, 5.5–5.79%, 5.8–6.0%, ≥6.1%). Knee extensor strength was significantly lower in the highest quartile compared with the lowest quartile after adjustments for age, race, sex, weight and height, and physical activity. Interestingly, an additional adjustment for peripheral neuropathy moderately attenuated the statistical significance. Muscle quality (muscle strength/muscle mass) was also poorer in the highest HbA1c quartile, whereas muscle mass was not significantly different over time among the groups stratified by HbA1c. Interestingly enough, the difference in muscle strength between the higher and lower HbA1c groups seemed to start in patients as young as in their 40s. These results suggest that hyperglycemia-associated muscle functional loss starts in the very early stage of type 2 diabetes mellitus, and in later stages diabetic peripheral neuropathy might accelerate the reduction in muscle strength. Hyperglycemia affected muscle strength and quality, but not

mass itself in the current study. The results of the current study could suggest that hyperglycemia might induce mitochondrial dysfunction, and that peripheral neuropathy is also related to reduced muscle strength in older patients with diabetes mellitus. The reduction of muscle mass might be associated with factors other than hyperglycemia itself in diabetes mellitus. The present study was observational, and provides limited insight in terms of elucidating the mechanism underlying hyperglycemia and muscle function decline. Future investigations are required to shed light on this mechanism.

Sarcopenia/frailty is highly associated with geriatric syndrome and poor outcomes. As the worldwide population continues to age, the number of older persons with diabetes mellitus is increasing. The problem of sarcopenia/frailty will continue to increase in importance in an aging society.

Several studies have suggested that blood glucose-lowering therapy with insulin sensitizers (metformin and/or thiazolidines) could improve muscle function or attenuate the loss of muscle mass. It has been well-established that good blood glucose control prevents the development of microangiopathy, including neuropathy, which has been suggested to be involved in the diabetes mellitus-related reduction of muscle strength.

Considering its high prevalence in diabetic patients, such patients might be screened for sarcopenia/frailty in middle age and beyond. Despite the recent increment of interest in this issue and the large number of findings related to this issue that have been accumulated, there

is no cure for sarcopenia/frailty. Thus, improving the prevention and treatment of sarcopenia/frailty is an urgent issue in our society. The treatment of diabetes mellitus at an early stage might help prevent the development of sarcopenia/frailty and possibly geriatric syndrome (Figure 1). Further exploration of the etiology of the incidence of sarcopenia/frailty in diabetes should be performed, and clinical trials focusing on this issue should be pursued. Helping patients with diabetes mellitus maintain their functional activity would provide them with a better quality of life and more successful aging. A greater accumulation of data regarding this issue is warranted.

## DISCLOSURE

The author declares no conflict of interest.

Hiroyuki Umegaki\*

Department of Community Healthcare  
and Geriatrics, Nagoya University  
Graduate School of Medicine, Nagoya,  
Aichi, Japan

## REFERENCES

1. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, *et al.* Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. *Age Ageing* 2010; 39: 412–423.
2. Fried LP, Tangen CM, Walston J, *et al.* Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci* 2001; 56: M146–M156.
3. Kim TN, Park MS, Yang SJ, *et al.* Prevalence and determinant factors of sarcopenia in patients with type 2 diabetes: the Korean Sarcopenic Obesity Study (KSOS). *Diabetes Care* 2010; 33: 1497–1499.
4. Morley JE, Malmstrom TK, Rodriguez-Mañas L, *et al.* Frailty is also higher in the prevalence in older with DM. *J Am Med Dir Assoc* 2014; 15: 853–859.
5. Kalyani RR, Metter EJ, Egan J, *et al.* Hyperglycemia predicts persistently lower muscle strength with aging. *Diabetes Care* 2015; 38: 82–90.

Doi: 10.1111/jdi.12365