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COMMENTARY

Clinical impact of sarcopenia and dynapenia on diabetes

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Abstract
Sarcopenia as a progressive and generalized skeletal muscle disorder that is associated with an increased likelihood of adverse outcomes, including falls, fractures, physical disability, and mortality. On the other hand, an age-related decline in muscle strength prior to the reduction of muscle mass, is proposed to be "dynapenia". Sarcopenia and dynapenia have recently been recognized as a diabetic complications in type 2 diabetes. We firstly indicated that sarcopenia was frequently observed in 16.6% of patients with type 1 diabetes aged even over 40 years. Additionally, we recently reported that the prevalence rate of dynapenia was higher than sarcopenia in patients with type 2 diabetes. Chronic hyperglycemia accelerates accumulation of advanced glycation end products (AGEs), which causes diabetic vascular complications through oxidative stress and chronic inflammation. We also demonstrated that skin autofluorescence (AF) as a marker of AGEs, was the independent determinant for skeletal muscle mass and strength in patients with type 2 diabetes and muscle strength in type 1 diabetes. Therefore, the early diagnosis of muscle weakness is essential for patients with diabetes and sustained good glycemic control with exercise and dietary intervention might be beneficial to prevent the progression of muscle weakness in these patients.

Keywords Sarcopenia · Dynapenia · Diabetes · Elderly

Sarcopenia and dynapenia

Pandemic increase in the number of elderly patients with diabetes mellitus is a social and economic burden, as well as a medical issue. Elderly patients with diabetes mellitus have multiple complications, such as advanced vascular disease and impaired cognitive function. Recently, ageing-related muscle weakness, so-called sarcopenia, has been recognized as a diabetic complication and frequently increases the incidence of falls and frailty in these patients [1, 2]. Sarcopenia was proposed as an ageing-related loss of muscle mass and function by Rosenberg IH in 1988 [3].

On the other hand, Clark BC and Manini TM proposed that an ageing-related decline in muscle strength prior to the reduction of muscle mass should be described as "dynapenia" [4]. To evaluate muscle strength, they recommended knee extension strength as well as grip strength simultaneously. 'Sarcopenia' should be used in its original context, the loss of skeletal muscle mass, while the term 'dynapenia' should be used to represent the impaired muscle strength without loss of skeletal muscle mass.

We observed a high prevalence rate of low knee extension strength as well as sarcopenia in type 1 diabetes [5]. Moreover, we recently reported that the prevalence rate of dynapenia was higher than sarcopenia in patients with type 2 diabetes [6]. In addition, the prevalence of poor muscle strength has been found to be higher in patients with type 1 and 2 diabetes, than in the general elderly Japanese population [7]. Taken together, muscle strength could be impaired prior to reduced muscle mass in patients with type 1 and 2 diabetes.

New definition of sarcopenia: EWGSOP2

The definition of sarcopenia was established by the European Working Group on Sarcopenia in Older People (EWGSOP) [8] and the Asian Working Group of Sarcopenia (AWGS) in 2010 and 2014, respectively [9]. EWGSOP defines sarcopenia as a progressive and generalized skeletal muscle disorder that is associated with an increased

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likelihood of adverse outcomes, including falls, fractures, physical disability, and mortality [10–12]. In these criteria, sarcopenia is identified by decreased muscle mass accompanied by decreased grip strength or gait speed. The determinants for sarcopenia, proposed by EWGSOP and AWGS, are hand-grip strength, gait speed, and skeletal muscle mass index (SMI). An updated definition of sarcopenia proposed by EWGSOP2 in 2018 (Fig. 1) [13], added the chair stand test, instead of gait speed, as indicator of muscle strength, and the gait speed was categorized as measurement tool of physical performance in clinical practice. Hand-grip strength has been widely used as a diagnostic criterion and correlates well with most relevant outcomes. Although the diagnostic criteria of AWGS and EWGSOP did not include lower limb muscle weakness [8, 9], the chair stand test was added to evaluate the lower limb muscle weakness in clinical practice in EWGSOP2 [13]. Since the cost, availability, and usability are important to determine measurement tools in clinical practice, the chair stand test is better indicator than accurate knee flexion/extension measurement tools which is necessary to use special equipment and training.

Sarcopenia and diabetes

According to AWGS criteria, the prevalence of sarcopenia is 4–11% in Asian individuals over 65 years, whereas 11–15% in patients with type 2 diabetes [6, 14, 15]. We also indicated that sarcopenia was frequently observed even in 16.6% of patients with type 1 diabetes aged over 40 years [5]. In addition, many of these patients presented with reduced muscle function, involving lower SMI and limb muscle strength. The influence of type 1 diabetes on skeletal muscle mass has been analyzed in humans and rodent's models [16, 17]. These results clearly showed that type 1 diabetes was associated with impaired skeletal muscle mass and strength. Hormonal changes of decreased insulin and IGF-1 signaling, and increased glucocorticoid were speculated to contribute to muscle atrophy in these patients. Recent study also revealed that hyperglycemia itself reduces muscle mass via increase of KLF15 in myocyte [18]. Therefore, patients with diabetes are possible candidates for disease-related sarcopenia.

Since hyperglycemia itself has been proposed to be a contributor of sarcopenia, treatment for diabetes could be preferable to prevent and attenuate loss of muscle mass and function accompanied with diabetes. In addition, treatment with insulin [19] and dipeptidyl peptidase 4 (DPP-4) inhibitors [20] was reported to attenuate progression of sarcopenia

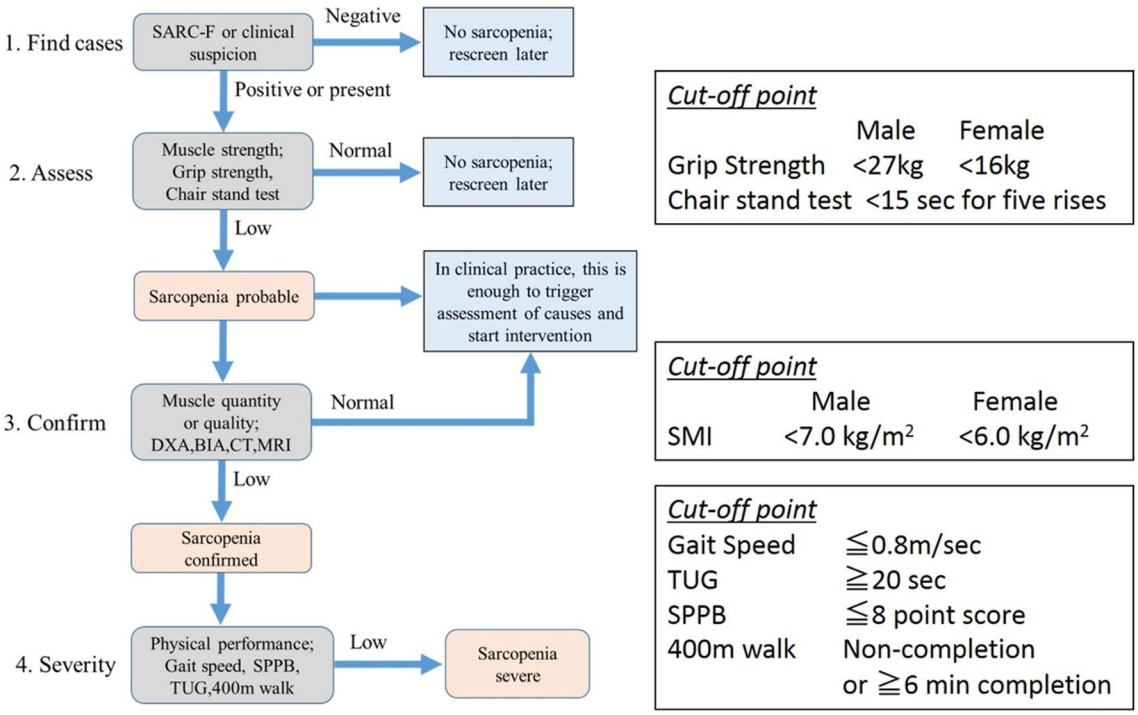

Fig. 1 Updated algorithm for sarcopenia case finding, diagnosis, and severity determination by EWGSOP2 (*DXA* dual energy X-ray absorptiometry, *BIA* bioelectrical impedance analysis, *SMI* skeletal muscle mass index, *TUG* timed up and go test, *SPPB* short physical performance battery)

in patients with type 2 diabetes. Sodium–glucose cotransporter 2 (SGLT2) inhibitors also reported to increase hand-grip strength [21], but several reports have been showed that SGLT2 inhibitor decrease muscle mass as well as fat mass and body weight. Therefore, the use of SGLT 2 inhibitors should be carefully in elderly patients with sarcopenia, and the further studies need to clarify this issue.

Dynapenia and diabetes

Dynapenia, characterized by muscle mass weakness independent of muscle mass, was defined according to the proposed criteria based on low hand-grip strength and knee extension strength with normal SMI (Fig. 2) [4]. When the sarcopenia components were examined individually, only a low muscle strength was associated with the incidence of recurrent falling, independent of low muscle mass or slow gait speed [22]. Therefore, in elderly individuals, muscle strength could be more beneficial tool to evaluate physical condition than gait speed and muscle mass. The previous report showed that hyperglycemia evaluated by glycated hemoglobin (HbA1c) is associated with the weakness of muscle strength independently with muscle mass [23]. In addition, the decline in muscle strength in highest quartile of HbA1c groups seemed to start at 40 years. This suggests that hyperglycemia-associated muscle weakness could start at an early stage of diabetes. Our study shows that sarcopenia and dynapenia were observed in elderly patients with a longer duration of diabetes, and the difference between the clinical characteristics of these comorbidities was adiposity, indicated by BMI, %fat, and visceral fat area [6]. Sarcopenic patients showed low BMI, whereas in dynapenia patients, BMI was comparable to that in patients without sarcopenia and dynapenia. A previous study showed that obese patients with type 2 diabetes had lower muscle strength than healthy subjects with normal body weight [2]. The accumulation of intramuscular fat is inversely associated with lower limb muscle function in elderly individuals [24]. On the other hand, increased body weight could be detrimental to the maintenance of muscle volume. Indeed, a high %body fat was significantly, and independently, associated with the risk of dynapenia in patients with type 2 diabetes in our study. Elderly, obese patients with type 2 diabetes may, therefore, have a higher prevalence of dynapenia, but not sarcopenia. Diabetic polyneuropathy might cause a decline in lower extremity strength in middle-aged and elderly type 2 diabetes patients [25]. In addition, 38.8–62.4% of patients with type 2 diabetes aged ≥ 65 years demonstrated low hand grip and knee extension strength, respectively, in our study, and this prevalence was higher than that found in the general elderly Japanese population [7]. It is possible that type 2 diabetes may lead to muscle weakness at a younger age than the general population. Therefore, the typical characteristics of muscle dysfunction in elderly patients with type 2 diabetes could be lower muscle strength in the extremities, but not a decrease in muscle volume compared to subjects without type 2 diabetes. Furthermore, impaired knee extension

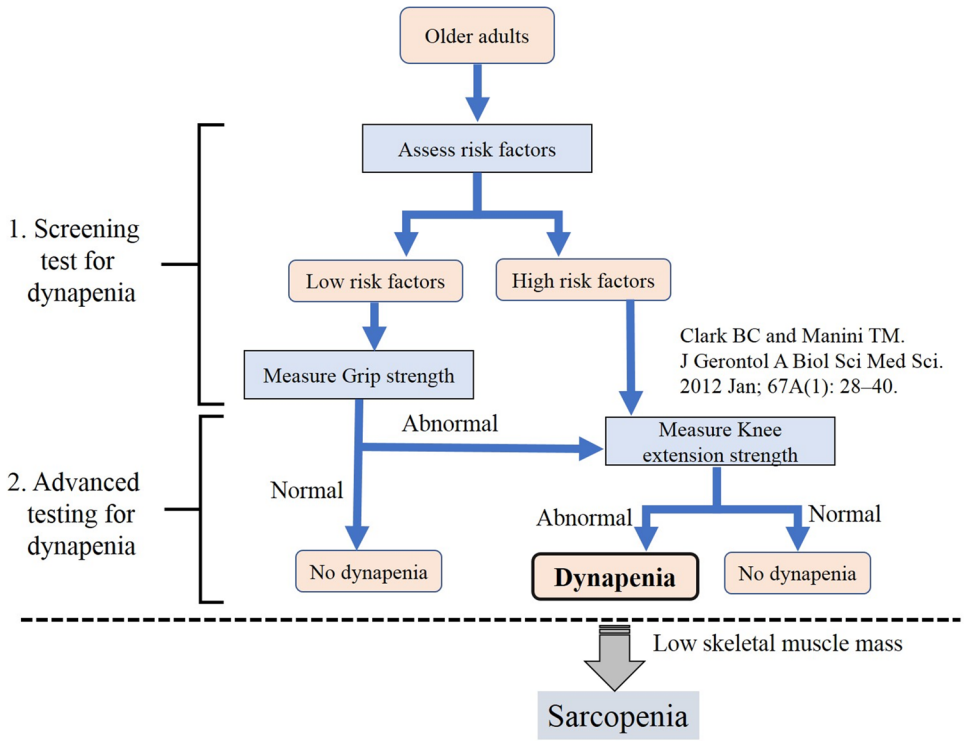

Fig. 2 Algorithm for diagnosis of dynapenia

strength was observed frequently even in patients under 65 years, suggesting that muscle strength of lower limb could be a better indicator of muscle dysfunction than grip strength, in patients with type 2 diabetes. Therefore, a clear definition of dynapenia will provide a better understanding of the role that dynapenia plays in the loss of physical function and increased risk for disability among older adults.

Advanced glycation end products and sarcopenia and dynapenia in diabetes

Advanced glycation end products (AGEs) accumulate with ageing in various human tissues. Chronic hyperglycemia also accelerates AGEs' accumulation, which causes diabetic vascular complications such as macro- and micro-angiopathy through oxidative stress and chronic inflammation [26]. As well as a longer duration of diabetes, sustained hyperglycemia is thought to contribute to muscle weakness in patients with diabetes [23]. AGEs have been identified in ageing human skeletal muscle. Skin autofluorescence (AF), indicator of accumulated AGEs in the skin, is known to reflect the integration of long-term glycemic control over the past 15 years, but not current glycemic control, in patients with type 1 diabetes [27]. We previously indicated that skin AF was inversely associated with low knee extension strength in type 1 and 2 diabetes patients using an adjusted multivariate logistic regression model [5, 6]. Skin AF was also inversely associated with low SMI in type 2 diabetes patients using this model. Recent study in the rodent demonstrated that AGEs induced muscle atrophy and muscle dysfunction via AGE receptor-mediated AMPK-downregulation of the Akt-signaling pathway [28]. Therefore, ageing and sustained hyperglycemia accumulate AGEs in the muscle, and reduce muscle strength and muscle mass in patients with diabetes.

Conclusion

Patients with type 1 and type 2 diabetes are possible candidates for dynapenia as well as disease-related sarcopenia. In addition, we revealed that the weakness of knee extension strength was highly associated with accumulation of AGE even under 65 years in the both type of diabetes. Therefore, chronic hyperglycemia-associated decline of muscle strength begins at younger stage of type 1 and type 2 diabetes. Therefore, the early diagnosis of muscle weakness is essential for patients with diabetes and sustained good glycemic control with exercise and dietary intervention might be beneficial to prevent the progression of muscle weakness in these patients.

Compliance with ethical standards

Conflict of interest The author declares that they have no conflict of interest.

Ethical standard This article does not contain any studies with human or animal subjects performed by the author.

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