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UPDATE

Sarcopenia in elderly diabetes

Sarcopenia represents the progressive loss of muscle mass and function during aging. The most widely accepted definition of sarcopenia is proposed by the European Working Group of Sarcopenia in Older People, which combines muscle mass, strength and physical performance as required criteria for diagnosis. The Asia Working Group for Sarcopenia definition is similar, but provides modified criteria for Asian people[1]. The prevalence of sarcopenia ranges from 10 to 40% in people aged ≥65 years[2].

Type 2 diabetes is a highly prevalent health problem in the elderly, affecting >25% of people aged >65 years. Older adults with diabetes are known to have a higher rate of functional decline and disability[3]. In older adults with diabetes, sarcopenia has recently been recognized as another comorbidity[4].

Several studies showed that the muscle mass index and muscle strength were lower in older patients with diabetes than those without diabetes[5]. Older adults with diabetes have been reported to have lower handgrip strength[6]. Greater loss in thigh muscle was also observed in older women with diabetes compared with the non-diabetes population[7]. A recent meta-analysis showed that the prevalence of sarcopenia is higher in the diabetes group in respect to normoglycemic controls[8]. Lower body mass index (<24 kg/m^2) and longer duration of diabetes were reported to increase the risk of sarcopenia in people with diabetes[9,10].

In contrast, sarcopenia might also increase the risk of developing diabetes among older people. Individuals with low skeletal muscle mass have greater risk of developing diabetes compared with those with higher muscle mass. Coexistence of low muscle mass and obesity contributed to an even higher risk of diabetes[1].

PATHOGENESIS

Diabetes has been reported to accelerate the reduction of muscle mass and strength by several mechanisms. Protein synthesis is stimulated by insulin, and impairment in the insulin-associated signaling pathway might lead to reduced muscle anabolism and increased protein catabolism, which contribute to sarcopenia[11].

Furthermore, hyperglycemia increases the production of advanced glycation end-products. The accumulation of advanced glycation end-products in the muscle causes deterioration of muscle function by increasing intramuscular protein cross-linking, interfering the muscle contractility, upregulating inflammation, developing oxidative stress and impairing endothelium function, all of which might lead to sarcopenia[12].

The major causes of sarcopenia include insufficient nutrition intake, inadequate physical activities, and declined hormonal and neuromuscular function[11]. Patients with peripheral neuropathy have more intermuscular adipose tissue, which is associated with poor muscle strength and function. Inflammatory markers, such as tumor necrosis factor and interleukin-6, were negatively associated with muscle mass, strength and physical performance[13].

GLUCOSE-LOWERING MEDICATIONS AND SARCOPENIA

Various glucose-lowering medications might have different effects on the muscle metabolism. Currently, the most widely used glucose-lowering drugs included metformin, thiazolidinediones (TZDs), sulfonylureas, dipeptidyl peptidase-4 inhibitors, glucagon-like peptide-1 receptor agonists, sodium–glucose cotransporter 2 inhibitors (SGLT2i) and insulin.

Metformin activates the adenosine monophosphate-activated protein kinase (AMPK) pathway, which upregulates fatty acid oxidation and reduces intramuscular lipid accumulation. In contrast, however, AMPK also inhibits the mechanistic target of rapamycin, which plays a key role in muscle growth, so activation of the AMPK pathway might also lead to a possible decrease in muscle protein synthesis. Current clinical trials showed inconsistent conclusions about the effects of metformin on sarcopenia[14].

TZDs activate peroxisome proliferator-activated receptor-γ, which facilitates the attenuation of insulin resistance. TZDs also activate the AMPK pathway and thus promote fat oxidation in skeletal muscles. However, data from clinical trials investigating the effects of TZDs on sarcopenia are still limited and the results are conflicting[15].

Sulfonylurea induces atrophy in rat skeletal muscle mass. The caspase-3-dependent or independent pathways might participate in the activation of atrophy signaling in muscles. Muscle atrophy was observed in 0.27% of the diabetes patients receiving glibenclamide or glyburide, compared with 0.02% in individuals using medications other than sulfonylureas in an observational study[14].

A cross-sectional study showed that parameters associated with sarcopenia, such as skeletal muscle mass, muscle strength and gait speed, were better in people with type 2 diabetes taking dipeptidyl peptidase-4 inhibitors compared with sulfonylureas[16]. Another study also reported that skeletal muscle mass increased significantly in overweight people with type 2 diabetes receiving dipeptidyl peptidase-4 inhibitors compared sulfonylurea after 24 weeks of treatment[17].

Recently, several clinical trials aimed to investigate the effects of SGLT2i on sarcopenia. Dapagliflozin was shown to significantly decrease skeletal muscle mass in people with type 2 diabetes and non-alcoholic liver disease after 24 weeks of treatment compared with the standard

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treatment group[18]. Other studies showed that luseogliflozin caused a significant reduction in skeletal muscle mass and skeletal muscle mass index after 12–36 weeks of treatment[19]. A Japanese open label study of ipragliflozin and metformin showed a non-significant decrease in abdominal muscle, and an increase in handgrip strength while combined with sitagliptin[20]. A study showed that tofogliflozin is associated with a significant decrease in skeletal muscle mass after 12 weeks of treatment in people with type 2 diabetes[21]. These studies consistently showed that SGLT2i could increase the risk of sarcopenia in diabetes patients.

Most studies with glucagon-like peptide-1 receptor agonists did not show significantly reductions in muscle mass or worsening sarcopenia parameters in diabetes patients. A study with liraglutide did not show decreased muscle mass or deteriorated parameters associated with sarcopenia in people with type 2 diabetes. Similarly, another study with exenatide did not show significant changes in skeletal muscle mass after 12 weeks of treatment[14].

Insulin therapy was shown to prevent a decrease in the skeletal muscle index of lower extremities in people with type 2 diabetes in a retrospective observational study[22]. Similarly, another study showed that patients taking glucose-lowering drugs have a greater decline in skeletal muscle index compared with insulin therapy. However, the time required to complete the Timed Up and Go test was significantly increased in the insulin group compared with patients taking oral glucose-lowering drugs[23]. Table 1 summarizes the effect of glucose-lowering medications on muscle mass in type 2 diabetes patients.

Table 1 | Effect of glucose-lowering medications on muscle mass in type 2 diabetes patients

Glucose-lowering medications	Effect on muscle mass
Metformin	Inconclusive[14]
Thiazolidinedione	Inconclusive[15]
Sulfonylurea	Decreases[14]
Dipeptidyl peptidase-4 inhibitors	Inconclusive/ increases[16,17]
Sodium–glucose cotransporter 2 inhibitors	Decreases[18,19,20,21]
Glucagon-like peptide-1 receptor agonists	Inconclusive[14]
Insulin	Inconclusive/ increases[22,23]

CONCLUSIONS

Sarcopenia represents an age-related loss of skeletal muscle mass and function, which has been shown to be one of the important comorbidities of diabetes. Type 2 diabetes contributes to the development of sarcopenia through various mechanisms, including impaired insulin-associated signaling pathways, accumulation of advanced glycation end-products, peripheral neuropathy and chronic inflammatory status. Sulfonylurea and SGLT2i should be cautiously prescribed for elderly diabetes patients. Further studies are required to elucidate the relationship between sarcopenia, type 2 diabetes and glucose-lowering medications.

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