

Sarcopenia, frailty circle and treatment with sodium–glucose cotransporter 2 inhibitors

To date, diabetes treatment has focused on the prevention of chronic complications as a result of microangiopathy and cardiovascular diseases, as well as acute complications with diabetic ketoacidosis and diabetic hyperosmolar hyperglycemic coma. Recently, the prevention of sarcopenia, a dysnutrition state accompanying aging or obesity in patients with diabetes, has become a new target of diabetes treatment.

Sarcopenia is characterized by reduced skeletal muscle mass and decreased muscle functions (i.e., muscular strength and performance) that are accompanied by a decrease in physical activity. It is a serious problem owing to the risk of falling and bone fractures, and the state-of-life prognosis, including risk of aspiration pneumonia from reduced swallowing ability or frailty. Frailty refers to a state wherein the vulnerability of the entire body is elevated, usually resulting from various pathological conditions, such as a decrease in mental and/or physical activity. Frailty can also occur from repeated severe hypoglycemia, associated with diabetes treatment. Once in the state of frailty, a patient can experience dysphagia as a result of muscle weakness in swallowing and exacerbation of anorexia, which can lead to further malnutrition. In this way, frailty based on sarcopenia forms a vicious cycle (Figure 1). Therefore, it is important to cut off this cycle through effective therapeutic interventions¹. Sarcopenia and frailty have, however, few early diagnostic methods, such as biomarkers, and therapeutic treatment so far. For the definition and diagnostic criteria of sarcopenia, consensus by the European Working Group on Sarcopenia in Older People was announced in 2010². The body composition of an average Asian person is apparently different from that of a European person; hence, the diagnostic criteria of sarcopenia for Asian people should be independently developed. With this perspective, consensus by the Asian Working Group on Sarcopenia in Older People was subsequently announced in 2014³. In these consensus, sarcopenia was originally determined based on the data obtained by dual-energy X-ray absorption method. In recent years, the bioelectrical impedance method has gained popularity as a simplified method, although its evaluation remains to be established owing to accuracy errors.

In addition to age-related or primary sarcopenia, dysnutrition based on metabolic syndrome with visceral fat accumulation and decreased muscle mass, regardless of age, has been recognized as secondary sarcopenia. It has been shown that patients with poorly controlled glycemia of diabetes have significantly less muscle volume⁴. Furthermore, the possibility that this muscle loss might be exacerbated even by diabetes treatment has

been indicated when measured as total lean mass⁵. It has been recently clarified that sodium–glucose cotransporter 2 (SGLT2) inhibitors show excellent effects in treating type 2 diabetes not only by correcting hyperglycemia and reducing the risk of cardiovascular events, but also by reducing the body fat mass, including visceral fat. Symptoms based on insulin resistance should be therefore further alleviated by this decrease in visceral fat mass. The mechanism for such a reduction in fat mass with the use of SGLT2 inhibitor is believed to be a result of lipolysis in the adipose tissue due to activation of gluconeogenesis (Figure 2). There is a concern, however, that the activation of the gluconeogenic system should induce not only lipolysis in the adipose tissue, but also proteolysis in the skeletal muscle that supplies amino acids to the liver as a substrate and can therefore lead to sarcopenia.

To address this issue, we carried out a clinical study⁶ using luseogliflozin, an SGLT2 inhibitor, for patients with Japanese type 2 diabetes who had an average body mass index of 28 kg/m². The mean change in the lean body mass was -0.79 kg at week 24 compared with that at baseline, and it was -0.99 kg at week 52 of treatment, which is a significant decrease. In addition, we measured the skeletal muscle index (SMI), which estimates the whole-body skeletal muscle mass more accurately than the total lean body mass. We did not find any significant change at week 24 by SMI, albeit a significant decrease of -0.151 kg/m² muscle mass was detected at week 36, followed by a decrease of -0.155 kg/m² at week 52 with no further decline. The proportion of the body composition was, however, favorably changed. Unlike the changes in bone mineral content, which did not detect any significant change at week 52, SMI was considered to be most likely influenced by the use of an SGLT2 inhibitor, because the decrease in SMI became significant after 36 weeks from the initiation of SGLT2 inhibitor treatment. A report on the other study with canagliflozin, another SGLT2 inhibitor, was also made in which SMI also showed similar trends⁷.

As mentioned earlier, it is an extremely important finding in clinical diabetes practice that the reduction of skeletal muscle mass can occur during treatment with SGLT 2 inhibitors, although the reduction is small. This finding raises questions on the effective means of preventing muscle loss and sarcopenia.

It is estimated that diabetes mellitus might soon become a highly frequent disease among the elderly and individuals with restricted physical activity. Thus, establishing new guidelines for diet therapy and exercise applicable to type 2 diabetes is critical.

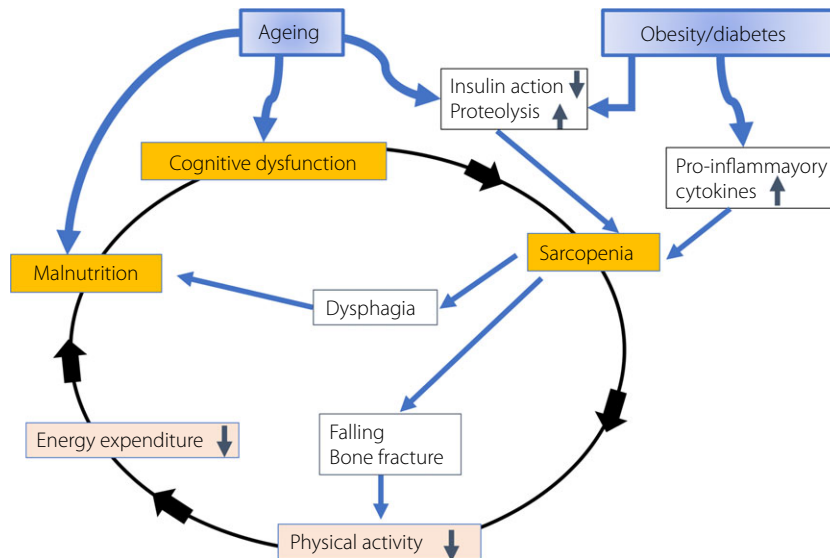


Figure 1 | The frailty cycle. Hormonal and nutritional change with aging causes malnutrition. In addition, a loss or decrease in function of insulin causes proteolysis in skeletal muscle. These conditions both lead to the frailty cycle, a vicious circle.

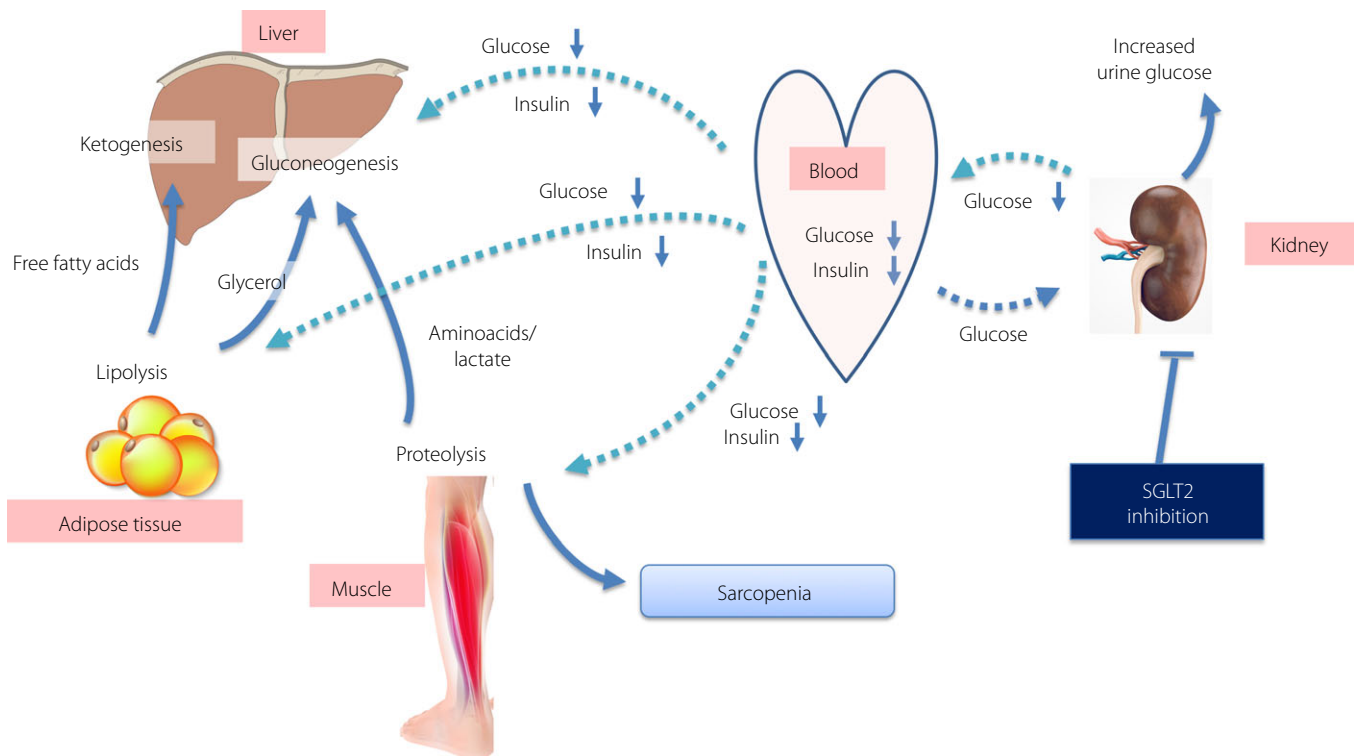


Figure 2 | Sarcopenia and sodium–glucose cotransporter 2 (SGLT2) inhibitors. Decreased serum insulin concentration causes a gluconeogenesis in liver and proteolysis in skeletal muscle. This process could cause sarcopenia if its extent is severe.

In fact, determining the nutritional content of a diet that can promote and induce insulin secretion after meals is urgent, and so is investigating the nutritional balance and types of exercise

required to maintain skeletal muscles. In this step, we are actively seeking such molecular research against sarcopenia for publication in our journal.

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