Sarcopenia, frailty and type 2 diabetes mellitus (Review)

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Abstract. Skeletal muscle is the largest and most energy-consuming organ in the human body, which plays an important role in energy metabolism and glucose uptake. There is a notable decrease in glucose uptake in the skeletal muscle of patients with type 2 diabetes mellitus (DM). Endurance exercise can reduce hyperglycemia and improve insulin resistance in patients with type 2 DM. Insulin exerts a variety of effects, many of which are mediated by Akt, including increasing glucose uptake, promoting glycogen synthesis and inhibiting glycogen degradation, increasing free fatty acid uptake, increasing protein synthesis, promoting muscle hypertrophy and inhibiting protein degradation. Skeletal muscle mass progressively declines with aging, resulting in loss of muscle strength and physical function. Sarcopenia is a syndrome characterized by loss of skeletal muscle mass and muscle weakness or loss of physical function, and frailty is another syndrome that has received great interest in recent years. Decreased organ function results in vulnerability to external stress. Frailty is associated with falls, fractures and hospitalization; however, there is the reversibility of returning to a healthy state with appropriate interventions. Frailty is classified into three subgroups: Physical frailty, social frailty and cognitive frailty, whereby sarcopenia is the main component of physical frailty. The present review discusses the associations between sarcopenia, frailty and type 2 DM based on current evidence.

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Abbreviations: IR, insulin resistance; DM, diabetes mellitus; IGF-1, insulin-like growth factor-1; EWGSOP, European Working Group on Sarcopenia in Older People; AWGS, Asian Working Group for Sarcopenia; LC, liver cirrhosis; GLUT4, glucose transporter 4; PGC-1α, peroxisome proliferator-activated receptor-γ coactivator-1α; BCAA, branched-chain amino acid; DXA, dual-energy X-ray absorption; OR, odds ratio; BMI, body mass index; HOMA-IR, homeostasis model assessment of insulin resistance; AMPK, AMP-activated protein kinase; FBS, fasting blood glucose

Key words: skeletal muscle, sarcopenia, frailty, type 2 diabetes mellitus, insulin

Contents

1. Introduction

Animals, including humans, have been constantly exposed to the danger of starvation during the course of evolution. As a result, animals have acquired the ability to survive by storing excess energy in the form of fat and utilizing it in the starvation status (1,2). Ironically, however, in today's advanced society, where excessive energy intake and lack of exercise have become the norm, this mechanism has become the cause of obesity, muscle weakness and insulin resistance (IR), etc. (1,2).

Skeletal muscle is the largest organ in the human body and plays an important role in energy metabolism and glucose uptake. Skeletal muscle is the most energy-consuming organ in the human body, with a heat expenditure of 30% of the total body in the basal metabolism (3). In patients with type 2 diabetes mellitus (DM), there is a marked decrease in glucose uptake in the skeletal muscle (4,5). It is well known that moderate exercise increases energy expenditure, reduces obesity, and increases glucose metabolism, thereby preventing and improving type 2 DM. Skeletal muscle accounts for about 50% of the body weight, and about 15% of the circulating blood volume is supplied to the skeletal muscle at rest (6). Approximately 20% of the oxygen consumed by the entire body is consumed by the skeletal muscle. Glucose in the blood is transported to the skeletal muscle and metabolized by oxygen. Continuous aerobic exercise increases oxygen uptake and improves glucose metabolism in the skeletal muscle (6).

Endurance exercise can improve aerobic metabolism and thus can reduce hyperglycemia in patients with type 2 DM.

Aging-related changes in the body composition are characterized by the followings: (1) a 40% decrease in lean body mass and an increase in fat mass between the ages of 20 and 70 (7). (2) The overall fat mass increases between the ages of 20 and 70, but the peripheral fat tends to decrease compared to the central fat (7). (3) After the age of 70, both lean body mass and fat mass decrease (7). (4) Visceral fat increases with aging (8). (5) Fat is more likely to be deposited in the skeletal muscle and the liver (8). (6) Increased visceral fat is associated with impaired glucose metabolism, and intramuscular and intrahepatic fat deposition is associated with IR through the release of adipokines and free fatty acids (9). (7) Decreased skeletal muscle mass results in a decrease in the basal metabolism of 2-3% per decade after the age of 20, and 4% per decade after the age of 50 (10,11).

The effects of insulin and insulin-like growth factor-1 (IGF-1) can be roughly divided into metabolic and proliferative effects, with insulin mainly exerting the former. Insulin exerts a variety of effects, many of which are mediated by Akt, including increasing glucose uptake, promoting glycogen synthesis and inhibiting glycogen degradation, increasing free fatty acid uptake, increasing protein synthesis, promoting muscle hypertrophy, and inhibiting protein degradation (12,13). In addition, the mitogen-activated protein kinases (MAPKs) pathway promotes cell proliferation. Insulin, together with IGF-1, can increase skeletal muscle mass (12,13). In addition to skeletal muscle, liver and adipose tissue are important insulin target organs, and insulin signaling in these organs mainly promotes protein anabolism. Insulin signaling promotes lipid synthesis and inhibits lipid degradation in the liver and adipose tissue, leading to the storage of excess energy. Inhibition of glycogenesis in the liver is also an important role of insulin (12,13). Fat, on the other hand, contains more energy per equal weight than glucose and other substances (protein: 4.1 kcal/g, fat: 9.3 kcal/g, and glucose: 4.1 kcal/g), making fat the most suitable substance for storing large amounts of energy (14,15). Glycogen is a short-term form of energy storage, whereas fat is a long-term, high-volume form of storage (14,15). Amino acid intake is expected to inhibit muscle atrophy by inhibiting the degradation of skeletal muscle protein as well as promoting the synthesis of skeletal muscle protein (16-18).

Skeletal muscle mass progressively declines with aging, leading to a decline in muscle strength and physical function. In 1989, Rosenberg coined the term 'sarcopenia' (from the Greek words 'sarx' meaning muscle, and 'penia' meaning loss) to describe the loss of muscle mass associated with aging. The term 'sarcopenia' has been widely accepted, and sarcopenia is now defined as a condition associated with loss of skeletal muscle mass and muscle weakness or loss of physical function (19,20). Guidelines for sarcopenia of the European Working Group on Sarcopenia in Older People (EWGSOP) (21) and the Asian Working Group for Sarcopenia (AWGS) (22) were published in 2010 and 2014, respectively, and in 2016, the Japanese Society of Hepatology issued sarcopenia assessment criteria specific to liver disease (23). In addition, a revised EWGSOP guideline was issued in 2019 (24) and a revised AWGS guideline in 2020 (25). The etiology of sarcopenia is thought to involve several complex factors in addition to aging. These include changes in sex hormones, underlying diseases (i.e., secondary sarcopenia), myokines, IR, poor nutritional intake of proteins and other nutrients, and disuse syndrome due to reduced motor function caused by loss of skeletal muscle mass, etc. (23). Considerable attention has been paid to the relationship between type 2 DM-related IR and skeletal muscle (26). On the other hand, frailty, as well as sarcopenia, is another condition that has received much attention in recent years (20,27,28). Decreased organ function leads to vulnerability to external stress. A condition, in which acute stresses such as infections, surgeries and accidents make it easier for physical functions to decline with decreased organ function, is called frailty (27,28). Frailty is also associated with outcomes such as need for care, death, falls and fractures, and hospitalization, but it encompasses the reversibility of returning to a healthy state with appropriate interventions (27,28). Frailty can be divided into the three main categories: physical frailty, social frailty and cognitive frailty, and sarcopenia is the main component of physical frailty (29). As in the case of sarcopenia, much attention has been paid to the relationship between type 2 DM and frailty. This review outlines the relationship between sarcopenia, frailty and type 2 DM.

2. Type 2 DM and skeletal muscle

Skeletal muscle takes up more than 80% of the glucose in the peripheral tissues by insulin and uses it for energy or stores the excess energy as glycogen (30). In diabetic patients, the total utilization of insulin in the whole body is about half of that in healthy individuals, which is due to the reduced utilization in the skeletal muscle (30). In other words, skeletal muscle is the main target of insulin and the largest organ that utilizes blood glucose. Therefore, the loss of skeletal muscle mass due to sarcopenia leads to decreased glucose utilization by insulin (i.e., IR). Decreased physical activity due to decreased skeletal muscle mass is also responsible for decreased glucose and lipid metabolism in the skeletal muscle (29). In addition, it is reported that IL-6 secreted by skeletal muscle stimulates the secretion of glucagon like peptide-1 (GLP-1) during exercise, and exercise is also associated with changes in insulin and glucagon secretion (31,32). Liver cirrhosis (LC), which is considered to be a typical form of secondary sarcopenia because of its tendency to cause protein-energy malnutrition, is also associated with a high rate of IR (20,23,33-35). LC patients are characterized by postprandial hyperglycemia (33). The organ network between liver and skeletal muscle has recently received much attention (23).

The glucose transporter 4 (GLUT4) is important for the uptake of blood glucose into skeletal muscle cells (36). GLUT4 is normally intracellular, but upon stimulation of glucose uptake, it moves to the cell membrane and acts as a transport pathway for glucose uptake into the cell. When the stimulus subsides, GLUT4 returns to the cell and waits for another opportunity to mobilize. When insulin binds to insulin receptors on the surface of the cell membrane of skeletal muscle, intracellular signaling molecules such as IRS, PI3 kinase, and Akt are activated in turn (36). This information is ultimately transmitted to GLUT4 stores in the cell, resulting in glucose uptake. IR in patients with type 2 DM is thought to be due

to abnormalities in this signaling pathway (18,36). In patients with type 2 DM, glucose uptake in peripheral tissues by insulin is reduced. As mentioned earlier, decreased glucose uptake has been shown to originate primarily in the skeletal muscle among the organs of the body, and exercise is a powerful way to increase glucose uptake and improve IR (3). The effects of prolonged exercise, such as marathon running, include the conversion of skeletal muscle to red muscle, an increase in the number of mitochondria, and an increase in the amount of GLUT4 (36,37). Moderate exercise improves mitochondrial function and also increases the ability of blood glucose uptake by increasing GLUT4 levels (36,37). Activation of mitochondrial function increases the beta-oxidation of fatty acids, facilitating the processing of free fatty acids being released from adipose tissue and reducing the accumulation of triglycerides in the liver (38,39). Thus, moderate exercise can efficiently improve dysfunction in the skeletal muscle.

The protein peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α) plays an important role in increasing mitochondrial mass and is thought to be the key to improving the condition of lifestyle-related diseases by exercise (40). In other words, increased expression of PGC-1α causes increased mitochondria, change to red muscle, increased energy expenditure, and weight loss as seen in exercise (40). PGC-1α is highly expressed in organs with active metabolism, such as brown adipocytes, skeletal muscle, and liver, and is especially highly expressed in soleus muscle, which has many type I myofibers (described later) among skeletal muscles (41). It is known that PGC-1α expression is increased by sustained exercise (42,43). Mice overexpressing PGC-1α in the skeletal muscle (PGC-1α transgenic mice) showed increased slow-twitch troponin I, myoglobin, and mitochondrial mass (44), characteristics of type I and IIA myofibers (described later), as well as enhanced expression of branched-chain amino acid (BCAA) metabolizing enzymes (45), resulting in increased endurance exercise capacity. It has been reported that expression of PGC-1α improves insulin sensitivity in diabetic mouse models (46).

3. Type 2 DM and myofiber

Skeletal muscle can be roughly classified into the type I myofibers, which have a slow contraction rate, and the type II myofibers, which have a fast contraction rate and a strong contractile force (47). Type II myofibers can be further divided into the type IIA myofibers with high aerobic glycolytic capacity and the type IIB myofibers with low aerobic glycolytic capacity (47). Type I and IIA myofibers with high aerobic glycolytic capacity have higher mitochondrial density and activity, actively metabolize glucose and lipids, and are less fatigued during endurance exercise (48). Type IIB myofibers have low mitochondrial density and activity, and are mainly involved in anoxic glycolysis in the cytoplasm, making them suitable for exercise that requires instantaneous contraction such as short-distance running (48). The distribution of these myofibers varies from region to region in the body. In the deep layers close to the bone, the proportion of type I and IIA myofibers is higher, and in the superficial layers close to the skin, the proportion of type IIB myofibers is higher (48). The composition of myofiber types changes with various stimuli. For example, the proportion of type I and IIA fibers increases with continuous aerobic exercise (49). On the other hand, it is known that the percentage of type IIB myofibers is higher and the percentage of type I and IIA myofibers is lower in patients with type 2 DM (49). Therefore, increasing the proportion of type I and IIA myofibers may be an effective means of preventing type 2 DM by increasing the number of mitochondria and energy metabolism. The skeletal muscle in patients with type 2 DM has fewer capillaries, regardless of the type of myofiber (50).

4. Type 2 DM and sarcopenia

According to the data released by the Japan Ministry of Health, Labour and Welfare in 2017, there are 3.289 million people with type 2 DM in Japan, and one in five adults has impaired glucose tolerance. The global diabetic population in 2019 is about 463 million. The International Diabetes Federation predicts that the number of people with type 2 DM will approach 600 million by 2035. Previous reports (Asian subjects) using the AWGS criteria for the diagnosis of sarcopenia reported the frequency of sarcopenia in patients with type 2 DM to be 7-28.8% (51-67). Among these reports, the average HbA1c of the target patients was the lowest in the report by Fukuoka *et al* (average HbA1c=7.0) (66) and was the highest in the report by Murai *et al* (average HbA1c=9.5) (63).

A 6-year follow-up study of limb skeletal muscle mass using dual-energy X-ray absorption (DXA) in 2,675 elderly people aged 70-79 years reported that the amount of limb muscle mass loss in elderly people with type 2 DM was significantly greater than that in elderly people without type 2 DM (68). In a cross-sectional study in Indians, the prevalence of sarcopenia in patients with type 2 DM was higher than in controls with an odds ratio (OR) of 3.48 (69). A report from Netherlands found significant decrease in skeletal muscle mass and muscle strength in patients with type 2 DM, even after adjusting for age, body mass index (BMI), fasting glucose, HDL cholesterol, BCAAs, and protein intake (70). An analysis of 14,528 individuals in the National Health and Nutrition Examination Surveys III in the United States indicated that sarcopenia is involved in glucose metabolism independently of obesity, that this tendency is stronger in individuals younger than 60 years, and that loss of skeletal muscle mass is a predictor of the type 2 DM incidence (71). When 932 subjects aged 40 years or older were classified into sarcopenia and normal groups using DXA, HbA1c level in the male sarcopenia group were significantly higher than that in the normal group (72). Sugimoto *et al* (59) examined the relationship between HbA1c levels and the prevalence of sarcopenia in 2,813 subjects aged 40 years and older, and the summary of their results were: i) the prevalence of sarcopenia increased with increasing HbA1c levels, and these linear relationships were particularly marked in non-obese type 2 DM patients with a BMI <22.3 kg/m^2 (the prevalence of sarcopenia was: 7.0% in the HbA1c <6.5% group; 18.5% in the HbA1c 6.5-7.0% group; 20.3% in the HbA1c 7.0-8.0% group; and 26.7% in the HbA1c 8.0% or higher group), ii) higher HbA1c levels were more strongly associated with lower skeletal muscle index (OR=5.42) than lower grip strength (OR=1.89) or walking speed (OR=1.13),

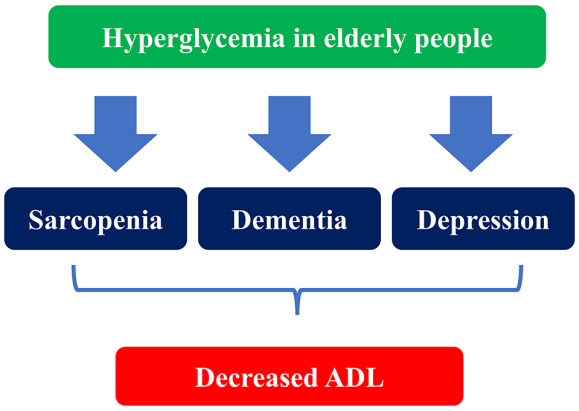

Figure 1. Hyperglycemia in elderly people is an aggravating factor for sarcopenia, dementia and depression, and declines ADL abilities. ADL, activities of daily living.

and iii) no association was found between blood glucose levels and the prevalence of sarcopenia in the elderly people with normal blood glucose levels (59). Lee *et al* (73) divided 3,132 elderly non-diabetic men aged 65 years or older into quartiles according to homeostasis model assessment of insulin resistance (HOMA-IR) levels, followed them for 5 years using DXA, and they found that elderly men with higher HOMA-IR had greater loss of limb skeletal muscle mass (73). These results suggest that aging-related muscle mass loss may affect HbA1c levels through reduced glucose utilization, or that increased IR may further contribute to sarcopenia by decreasing skeletal muscle protein synthesis and accelerating protein degradation. Hyperglycemia in the elderly is an aggravating factor for sarcopenia, dementia, and depression, and leads to ADL decline (74) (Fig. 1).

Sarcopenia is a risk factor for developing type 2 DM, and type 2 DM is a risk factor for developing sarcopenia (71,75). Regarding the mechanism, Ogawa's research group revealed for the first time that elevated blood glucose levels cause muscle mass loss through the action of two proteins, KLF15 and WWP1 (76). IR prevents the proliferation and growth of skeletal muscle cells, leading to a decrease in the skeletal muscle mass. They reported that in mice with type 2 DM, the amount of a transcription factor called KLF15 protein increases in the skeletal muscle as skeletal muscle mass decreases (76). KLF15 promotes skeletal muscle loss by increasing the expression of genes that cause skeletal muscle degradation and muscle atrophy. Their research confirmed that mice without KLF15 did not lose skeletal muscle mass in diabetes. They also found that (1) the degradation of KLF15 is inhibited by elevated blood glucose levels, (2) it is accumulated in the skeletal muscle, and (3) a protein called WWP1 plays an important role in regulating its degradation. WWP1 is one of the proteins called 'ubiquitin ligase', which binds ubiquitin to another protein. Proteins with large amounts of ubiquitin are degraded faster (77). Their study showed that WWP1 specifically binds ubiquitin to KLF15. When blood glucose levels increase, the amount of WWP1 is reduced, resulting in less ubiquitin binding to KLF15, which inhibits KLF15 degradation (76). The characteristics of the skeletal muscle in patients with type 2 DM are listed in Table I.

5. Glucose lowering drugs and sarcopenia

Sodium glucose co-transporter 2 (SGLT2) inhibitors are drugs that tilt the body toward a state of protein catabolism by increasing the amount of urinary glucose, which also reduces body fat, but at the same time reduces muscle mass because of the tilt toward protein catabolism (78,79). Metformin has been shown to inhibit sarcopenia (80-82). During acute exercise, enzyme activity increases to burn fat and carbohydrates to compensate for the large amount of energy consumed by the skeletal muscle. In this process, AMP-activated protein kinase (AMPK), which senses the energy status in the skeletal muscle, is activated (83,84). AMPK regulates energy metabolism in cells throughout the body. When the intracellular energy state becomes low energy (i.e., high AMP/ATP ratio) after exercise, AMPK is activated and sends GLUT4 out onto the cell membrane to take up glucose and break down fatty acids to obtain energy (83,84). Metformin activates AMPK (85). In other words, metformin takes glucose into the muscle cells by the same mechanism as the effect of exercise. Bouch *et al* (53) reported that in a comparison of sarcopenic and non-sarcopenic groups in patients with type 2 DM, the non-sarcopenic group had a significantly higher rate of metformin use (19% vs. 54%) (53). On the other hand, in a cohort study that followed changes in limb skeletal muscle mass in men aged 65 years and older for 3.5 years, limb skeletal muscle mass decreased by 4.4% in the group of diabetic patients who used drugs other than insulin sensitizers, while in the group that used insulin sensitizers, the decrease rate of limb skeletal muscle mass was 1.8% (86). Out of the previous reports using the AWGS criteria for the diagnosis of sarcopenia in Asians (mentioned earlier) (51-67), Sugimoto *et al* (59) reported the lowest frequency of sarcopenia (7%), and insulin preparations were used in about 70% of the non-sarcopenic patients in their study (59). On the other hand, Cui *et al* (58) reported the highest frequency of sarcopenia (28.8%), and insulin preparations were used in about 70% of sarcopenic patients. Ida *et al* (62) reported that the use of insulin preparations was significantly higher in the sarcopenia group compared to the non-sarcopenia group (79.5% vs. 62.1%). Thus, further investigations of the effect of insulin preparations on sarcopenia are needed.

6. Type 2 DM and frailty

The concept of frailty indicates 'a vulnerable state with reduced recovery to stress' and 'a condition that increases the risk of health problems, including falls, disability, and death'. In the elderly people, there is a risk that minor stresses may lead to changes in health status (e.g., from independent to needing care, from mobile to immobile, easily falling, from clear consciousness to delirium, etc.) that are disproportionate to the cause. It is important to take this into consideration during medical interventions (35,87).

Type 2 DM is thought to progress physical frailty and increase the risk of needing care and death through IR and inflammation (88), and clinical data supporting this relationship have been accumulated these days. Several prospective cohort studies and cross-sectional studies have reported the relationship between type 2 DM and frailty. In a prospective

Table I. Characteristics of the skeletal muscle in patients with type 2 diabetes mellitus.

No.	Characteristics
1	Decreased insulin-induced glucose uptake into the skeletal muscle.
2	Higher percentage of type IIB myofibers and lower percentage of type I and IIA myofibers.
3	Fewer capillaries regardless of myofiber type.
4	Decreased expression of proliferator-activated receptor-γ coactivator-1a and increased expression of Krüppel-like factor 15.

cohort study of non-institutionalized individuals aged 60 years or older (observation period, 3.5 years), type 2 DM increased the incidence of new cases of frailty (OR=2.18) (89). In a prospective study of subjects aged 65 years and older, type 2 DM was a significant risk factor for the progression from pre-frail to frailty, especially in patients with macrovascular diseases. Inappropriate lifestyle, abdominal obesity, and poor glycemic and lipid control were associated with the frailty progression, and dietary therapy reduced the risk (90). There are also reports that HOMA-IR is associated with the onset of frailty (91,92), and that frailty is associated with 2-hour blood glucose levels of 75 g oral glucose tolerance test (OGTT) (93,94). On the other hand≠, some longitudinal studies have shown that frailty is a risk factor for the development of type 2 DM, and type 2 DM and frailty can interact and form a vicious circle (95). In patients with type 2 DM, frailty can be a risk factor for pathological fracture (96). The presence of osteoporosis in female patients with type 2 DM predisposes to the development of frailty (97). Not only frailty but also pre-frail can be a poor prognostic factor in patients with type 2 DM (98).

Regarding the relationship between glycemic control and frailty, in a cross-sectional study of the Women's Health and Aging Study, the frequency of frailty was significantly higher in the group with HbA1c 6.5% or higher than in the group with HbA1c less than 6.0% (99), and in a longitudinal study, the frequency of frailty was 3.3 times higher in the group with HbA1c >8% than in the group with HbA1c <5.5% at baseline (100). In a community-based cohort study, higher 5-year mean blood glucose levels were associated with more frailty in non-diabetic patients, whereas a U-shaped association was found in diabetic patients. Baseline fasting blood glucose (FBS) <150 mg/dl (HbA1c=6.9%) had an OR of 1.41, and FBS >190 mg/dl (HbA1c=8.2%) had an OR of 1.30, indicating a higher incidence of frailty, however, the incidence of frailty was the lowest at FBS 170 mg/dl (HbA1c=7.6%) (101). A recent cross-sectional study of elderly diabetic patients in Japan showed that the lower the HbA1c level, the greater the risk of developing frailty (102). Therefore, low HbA1c may be a risk factor for developing frailty in patients with type 2 DM. The reason for this may be that strict glycemic control may lead to frailty via hypoglycemia. In the Japanese guidelines for the treatment of type 2 DM in the elderly, it states that there are no reports that show that good glycemic control inhibits or improves frailty. On the other hand, there are several reports on management goals for type 2 DM patients with frailty. In type 2 DM patients with frailty, there is a report that the group with HbA1c 8-8.9% had preserved ADL and lower risk of death compared to the group with HbA1c 7-7.9%, and caution against over-lowering of blood glucose level is needed (103). As elderly patients may not have hypoglycemic symptoms such as sweating or palpitations despite low blood glucose levels, hypoglycemia may be overlooked in the routine medical care, which is associated with the risk of frailty progression (74). As lifestyle-related diseases such as type 2 DM can be risk factors for frailty, it is important to strictly manage them at least in the middle age. However, it is important to note that in the old age, especially over the age of 75 with reduced physiological reserve, the adverse events associated with strict glycemic control can lead to frailty and even the need for nursing care. In the elderly, hypoglycemia, depression, dementia, and frailty form a vicious cycle through reduced physical activity and reduced dietary intake (74) (Fig. 2)

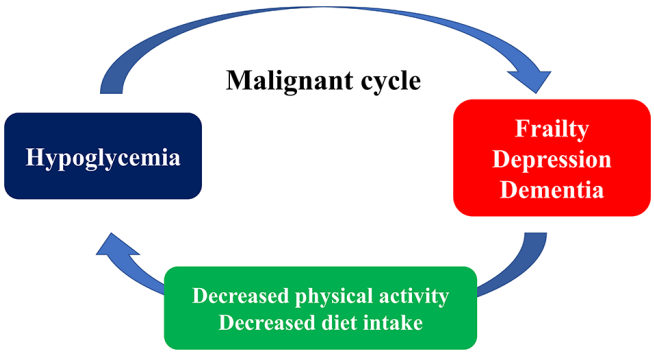

Figure 2. Hypoglycemia, depression, dementia and frailty reduce physical activity and dietary intake in elderly people.

7. Conclusion

The relationship between sarcopenia, frailty and type 2 DM was reviewed from the molecular biological and clinical perspectives. The frequency of type 2 DM increases with aging, and in Japan, about 20% of the population over the age of 70 suffer from type 2 DM. In an aging society, the association between sarcopenia or frailty and type 2 DM is an important issue. Skeletal muscles of diabetic patients have a different distribution of myofibers compared to healthy individuals. Hyperglycemia leads to the degradation of muscle proteins. There is a close relationship between the severity of type 2 DM and the frequency of sarcopenia. Hypoglycemia in diabetic patients with frailty should be carefully monitored. It is important to note that appropriate interventions in patients with sarcopenia or frailty can prevent the development of type 2 DM, and appropriate interventions in type 2 DM

patients can prevent the development of sarcopenia or frailty, which may lead to improved healthy life expectancy.

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HN drafted the initial manuscript. SF, AA, KY, HO, SN and KH edited and reviewed the manuscript. Data authentication is not applicable. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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