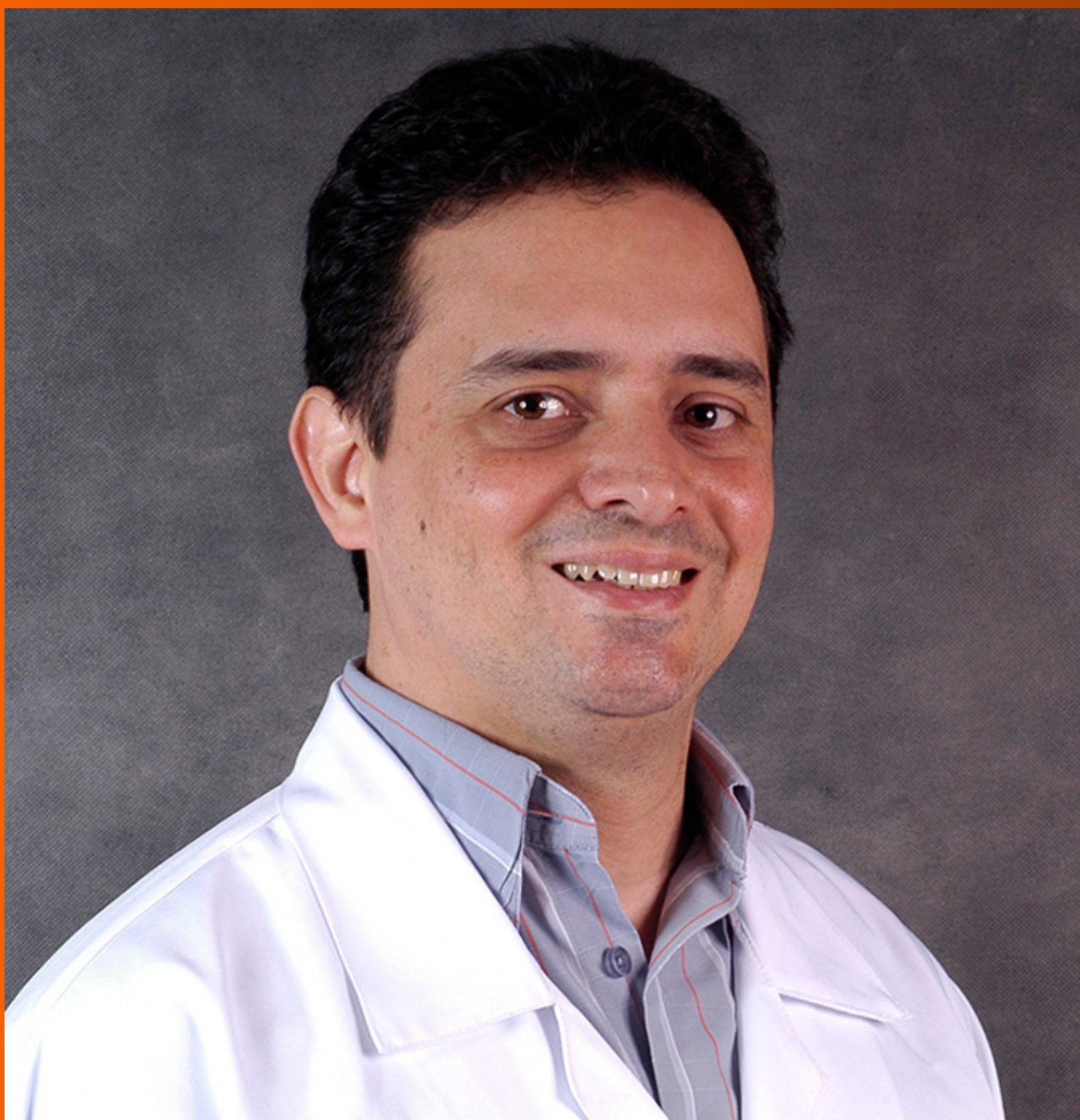


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Editorial Board Member of *World Journal of Diabetes*, José Carnevalheira, MD, PhD, Associate Professor, Faculty of Medical Sciences, University of Campinas, Campinas 13083, São Paulo, Brazil. jbcc@g.unicamp.br

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WJD mainly publishes articles reporting research results and findings obtained in the field of diabetes and covering a wide range of topics including risk factors for diabetes, diabetes complications, experimental diabetes mellitus, type 1 diabetes mellitus, type 2 diabetes mellitus, gestational diabetes, diabetic angiopathies, diabetic cardiomyopathies, diabetic coma, diabetic ketoacidosis, diabetic nephropathies, diabetic neuropathies, Donohue syndrome, fetal macrosomia, and prediabetic state.

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Exercise therapy for sarcopenia and diabetes

Seung-Taek Lim, Sunghwun Kang

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Seung-Taek Lim, Institute of Sports and Arts Convergence (ISAC), Inha University, Incheon 22212, South Korea

Seung-Taek Lim, Waseda Institute for Sport Sciences, Waseda University, Saitama 341-0018, Japan

Sunghwun Kang, Laboratory of Exercise Physiology, College of Art, Culture and Engineering, Kangwon National University, Chuncheon-si 24341, South Korea

Sunghwun Kang, Interdisciplinary Program in Biohealth-machinery convergence engineering, Kangwon National University, Chuncheon-si 24341, South Korea

Corresponding author: Sunghwun Kang, PhD, Professor, Laboratory of Exercise Physiology, College of Art, Culture and Engineering, Kangwon National University, 1 Kangwondaehak-gil, Chuncheon-si 24341, South Korea. 94psycho@kangwon.ac.kr

Abstract

Aging is characterized by the gradual deterioration of function at the molecular, cellular, tissue, and organism levels in humans. The typical diseases caused by changes in body composition, as well as functional decline in the human body's organs due to aging include sarcopenia and metabolic disorders. The accumulation of dysfunctional aging β cells with age can cause decreased glucose tolerance and diabetes. Muscle decline has a multifactorial origin, involving lifestyle habits, disease triggers, and age-dependent biological changes. The reduced function of β cells in elderly people lowers insulin sensitivity, which affects protein synthesis and interferes with muscle synthesis. The functional decrease and aggravation of disease in elderly people with less regular exercise or physical activity causes imbalances in food intake and a continuous, vicious cycle. In contrast, resistance exercise increases the function of β cells and protein synthesis in elderly people. In this review, we discuss regular physical activities or exercises to prevent and improve health, which is sarcopenia as decreased muscle mass and metabolic disorders as diabetes in the elderly.

Key Words: Elderly; Diabetes; Sarcopenia; Resistance exercise; Aging; Muscle

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Core Tip: Exercise or physical activity should be regularly performed even before aging begins, and muscle mass should be increased through resistance exercise. The protein intake necessary for protein synthesis during resistance exercise should also be maintained in elderly people and those with diabetes or/and sarcopenia.

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INTRODUCTION

Aging is characterized by the gradual deterioration of function at the molecular, cellular, tissue, and organism levels, and human age is a major risk factor for diseases, including cardiovascular disease, diabetes, osteoporosis, and cancer[1]. Also, gradual decreases in muscle mass, especially in the lower extremities, and increases in fat volume, especially visceral and intermuscular fat, are general body composition changes associated with aging[2]. The typical diseases caused by changes in body composition (decreased muscle mass and increased fat mass), as well as functional decline in the human body's organs due to aging, include sarcopenia and metabolic disorders. Moreover, according to a recent estimate by the International Diabetes Federation, 8.8% (425 million people) of the world's 20-79-year-old population suffered from diabetes in 2017, and the number is expected to rise to 9.9% (629 million people) in 2045[3].

Elderly has complex diseases, not single diseases. Most review studies focus only on a single disease. In addition, it has been suggested that sarcopenia in the elderly plays a pivotal role in the pathogenesis of the frailty and functional disorders in diabetes. Through this review, we discuss regular physical activities or resistance exercises to prevent and improve health, which are sarcopenia as decrease muscle mass and metabolic disorders as diabetes in the elderly.

CAUSES OF DIABETES DUE TO AGING

Several factors are involved in the high prevalence of type 2 diabetes (T2D) in elderly people: (1) In relation to aging, T2D is associated with the decreased function of β cells that secrete insulin and decreased insulin sensitivity[4]; and (2) changes in the body composition related to aging lead to changes in insulin sensitivity due to a decrease in the amount of lean body mass and an increase in the amount of body fat[5].

The pancreas is an essential organ with both endocrine and exocrine tissues and plays an essential function in maintaining nutrient metabolism homeostasis in the body[6]. The accumulation of dysfunctional aging β cells with age can cause decreased glucose tolerance and diabetes[7]. Telomeres shortened by aging were reported to impair β cell function and participate in β cell destruction in the late stage of T2D[8]. The deletion of aging β cells in mouse models of type 1 diabetes showed increased insulin secretion and preserved insulin secretion ability, providing a link between cell aging and severe insulin deficiency[9].

In addition, considering that pancreatic weight, total insulin content, island size, and average insulin levels do not change, impaired signal transmission due to glucose stimulation during the aging process could be a decisive cause[10]. Some evidence suggested that the activation of inflammatory pathways contributed to insulin resistance in elderly people[11]. For example, aging is associated with inflammatory conditions in metabolic tissues and the upregulation of inflammatory cytokines, such as tumor necrosis factor- α , interleukin-6 (IL-6), and IL-1 family members, which can directly interfere with insulin signaling pathways and cause metabolic dysfunction[12-14]. Aging toll-like receptor-4 deficient mice with reduced inflammatory responses showed decreased expressions of inflammatory markers and p16Ink4a (also known as CDKN2A) in adipose tissue and improved glucose tolerance compared to aging mice with intact inflammatory responses[15].

CAUSES OF SARCOPENIA DUE TO AGING

Muscles are the most necessary body components and play a pivotal role in maintaining a healthy life. Muscles are directly or indirectly related to muscle strength, energy, balance, and immunity. However, aging is a powerful vehicle for promoting sarcopenia[16,17]. It is known that basal metabolic rate decreases during the normal aging process. After the age of 30, it decreases at a rate of 3%-8% per

decade due to involuntary muscle loss. After the age of 50, approximately 1%-2% of muscle mass is lost per year. This rate increases to 3% per year after the age of 60, along with a decrease in strength of 1.5% annually[18,19].

Muscle loss has multiple factors, including lifestyle habits, disease triggers, and age-dependent biological changes. It is dealt with in the geriatric literature. However, it is starting to be studied in other areas dealing with the complexity of frail older persons. Testosterone levels gradually decrease with aging, and muscle protein synthesis and muscle mass can be reduced[20]. Growth hormone and insulin-like growth factor levels are also gradually and progressively decreased during normal aging. Such decreases are associated with decrease in muscle mass, not muscle strength[21,22].

The term sarcopenia was coined by Rosenberg[23] to describe the age-related reduction in muscle mass that occurred with advancing age. However, muscle quality and structure are very important for each individual. Valid measurements are needed to establish the power of muscle mass[24]. Thus, sarcopenia that appears in elderly people and can be defined as the pathological loss of skeletal muscle[25]. It is characterized by structural changes in muscles along with that accompany dysfunction of muscles or decreased muscle strength. Sarcopenia should be considered a geriatric syndrome since multiple contributing factors (the aging process, diet, bed rest, sedentary lifestyle, chronic diseases, and drug treatment[26-28]) can cause the loss of muscle mass and that leads to an impaired state of health [29,30].

Sarcopenia has a multiple factorial origin[31]. Lifestyle habits, including physical inactivity, rest, and malnutrition, are known to play an important role in most cases. In elderly people, changes in the endocrine system are, which is typical during the aging process. They can cause an imbalance between the anabolic process and the catabolic process[32], and a decrease of anabolic hormones (testosterone, estrogens, growth hormone, insulin-like growth factor-1)[33], changes in the renin-angiotensin system[34], and vitamin D deficiency[35]. Low-grade systemic inflammation associated with, typical of aging and chronic disease, also plays an important role in increasing inflammatory cytokines.

RELATIONSHIP BETWEEN GLUCOSE METABOLIC AND EXERCISE

Glucose absorption by skeletal muscle contraction is caused by the presence of glucose transporter type 4 on the surface membrane and by accelerated diffusion according to the internal diffusion gradient for glucose[36]. Thus, the main step in controlling glucose absorption in skeletal muscles is the transport of glucose through cell membranes, and insulin and contractions induced *in vivo* by acute exercise or electrical stimulation can mediate glucose absorption in muscles[37].

Both aerobic exercise training and resistance exercise training are well known for their ability to restore systemic glucose homeostasis in people with metabolic T2D disease[38]. The relationship between glucose metabolism control and aerobic or resistance or combined exercise for both male and female pre-diabetes or diabetes patients are as follows. Twelve weeks of aerobic physical activity (60 min/d, 3 d/wk at 55%-65% HRR of rhythmic physical activity) and 12 wk of resistance physical activity (60 min/d, 3 d/wk at 55%-65% of 1 RM of machine weight) significantly decreased glycated hemoglobin (HbA1c) levels in pre-diabetes elderly people[39]; 12 wk of aquatic exercise (50 min/d, 3 d/wk at a rating on the perceived exertion scale of 10-16) improved glycemic control and decreased HbA1c in type 2 diabetes mellitus (T2DM) elderly people[40]; 6 mo of combined exercise (30 min of moderate aerobic exercise and 10 min of resistance exercise at 50%-70% of 1RM) significantly decreased HbA1c levels in T2DM elderly people[41]; 14 wk of resistance exercise (45 min/d, 3 d/wk at 60%-80% of 1RM for 1-8 wk and 70%-80% of 1RM for 10-14 wk) reduced plasma HbA1c levels and increased muscle glycogen stores in elderly people[42]; 2 years of aerobic exercise (60 min/d, 3 d/wk at 60%-70% of the HRmax) and resistance exercise (50 min/d, 3 d/wk of 13 types of resistance training protocols) HbA1C levels and β cell function were exercise responses in elderly patients with pre-diabetes[43]; 6 mo of resistance exercise (55 min/d, 3 d/wk at 75%-85% of 1 RM) was effective in improving glycemic control as shown by greater decreases in HbA1c levels[44]; 6 wk of high-intensity exercise training (3 d/wk supervised program at over 85% HRmax) increased insulin sensitivity in patients with T2DM[45]; 12 wk of 3 types of physical training (resistance, aerobic, and combined; 60 min/d, 3 d/wk) increased insulin receptor substrate (IRS)-1 expression by 65% in the resistance group and 90% in the combined group of patients with T2DM[46]; 8 wk of resistance and aerobic exercise (50 min/d, 2-3 d/wk at 65%-70% of 1RM and 65%-70% HRmax) significantly decreased HbA1c levels in both exercise groups[47], and 16 wk of low-intensity resistance training (2 d/wk at using body weight) significantly decreased HbA1c levels [48]. Nine studies contained elderly with T2DM are summarized the latest resistance exercises from traditional resistance exercises in Table 1.

EXERCISE FOR THE TREATMENT OF SARCOPENIA AND DIABETES

Sarcopenia is the age-related loss of skeletal muscle mass and strength that develops slowly over

Table 1 Resistance exercise and diabetes

Ref.	Study population and intervention	Study outcome
Kim <i>et al</i> [39], 2022	36 elderly people with pre-diabetics; 12 wk of resistance physical activity (60 min/d, 3 d/wk at 55%-65% of 1RM of machine weight)	Decreased glycated HbA1c levels
Nuttamonwarakul <i>et al</i> [40], 2012	20 elderly people with T2D; 12 wk of aquatic exercise (50 min/d, 3 d/wk at a perceived exertion (RPE) rating of 10-16)	Improved glycemic control and decreased HbA1c
Tan <i>et al</i> [41], 2012	25 elderly people with T2D; 6 mo of combined exercise (30 min of moderate aerobic exercise and 10 min of resistance exercise at 50%-70% of 1RM)	Decreased HbA1c levels
Castaneda <i>et al</i> [42], 2002	62 elderly patients with T2D; 14 wk of resistance exercise (45 min/d, 3 d/wk at 60%-80% of 1RM for 1-8 wk and 70%-80% of 1RM for 10-14 wk)	Reduced plasma glycosylated hemoglobin levels and increased muscle glycogen stores
He <i>et al</i> [43], 2022	82 elderly people with pre-diabetes; 2 years of resistance exercise (50 min/d, 3 d/wk of 13 types of resistance training protocols)	HbA1C levels and β cell function were resistance exercise response
Dunstan <i>et al</i> [44], 2002	36 elderly people with T2D; 6 mo of resistance exercise (55 min/d, 3 d/wk at 75%-85% of 1RM)	Improving glycemic control and decreases HbA1c levels
Jorge <i>et al</i> [46], 2011	48 middle-aged adults with T2D; 4 groups: Aerobic ($n = 12$), resistance ($n = 12$), combined ($n = 12$), and control ($n = 12$); 12 wk of training (60 min/d, 3 d/wk)	IRS-1 expression increased by 65% in the resistance group and by 90% in the combined group in T2DM
Ng <i>et al</i> [47], 2010	25 elderly people with T2D; 8 wk of resistance (50 min/d, 2-3 d/wk at 65%-70% of 1RM)	Decreased HbA1c levels
Takenami <i>et al</i> [48], 2019	10 elderly patients with T2D; 16 wk of low-intensity resistance training (2 d/wk at using body weight)	Decreased glycated hemoglobin

HbA1c: Hemoglobin; IRS: Insulin receptor substrate; T2DM: Type 2 diabetes mellitus.

decades and becomes an important factor in disability in the elderly population[49]. Insulin resistance in muscle protein metabolism with aging appears to be responsible for insensitivity to mixed supplements, and the presence of insulin resistance in muscle protein metabolism with aging independent of glucose tolerance has been demonstrated in healthy elderly subjects without diabetes[50]. Thus, the higher prevalence of sarcoidosis in T2DM individuals may be explained by other mechanisms, and the anabolic action of insulin in skeletal muscle is well known and may be progressively lost in T2DM due to decreased insulin sensitivity associated with the disease[51]. The decrease in muscle strength in elderly diabetes patients may be due, in part, to the intrinsic impairment of muscle strength generation, and a decrease in insulin signaling leads to a decrease in protein synthesis and an increase in proteolysis, which may ultimately lead to a decrease in muscle mass[52].

Resistance exercise is traditionally performed to increase muscle mass. Resistance exercise has a beneficial effect on sarcopenia in the general elderly population and is effective in coping with muscle mass reductions and performance deterioration in elderly patients with T2D[53,54]. Importantly, resistance exercise has also been found to have a beneficial effect on blood sugar profiles and insulin sensitivity[55]. In particular, in the case of elderly people, exercise is essential for preventing and managing sarcopenia because it counteracts the decline in both aging and muscle weakness caused by diabetes[56].

Compared to females who reported performing no strength training, females who performed strength training showed a 30% reduction in T2D (hazard ratio = 0.70, 95% confidence interval: 0.61-0.80)[57]. Short-term acute (2 d) moderate-intensity resistance exercise (50% of 1 RM) effectively reduced blood glucose levels and blood glucose fluctuations in elderly patients with T2M and sarcopenia[58]. Table 2 summarizes the benefit of resistance exercise in elderly people with sarcopenia.

Aging can accelerate the loss of muscle mass and function, and the loss of muscle mass and function may impair glucose metabolism and aggravate diabetes[59]. For this reason, elderly people especially, need to increase muscle mass, and the only way to increase muscle mass is to perform resistance exercises. The inclusion of gradual resistance exercise in lifestyle modification programs should be considered for elderly patients with sarcopenia and T2D or both[58,60]. There is also a general consensus that a moderate increase in daily protein intake to 0.8 g/kg/d or more in elderly people may enhance the metabolism of muscle proteins and reduce the progressive loss of muscle mass with aging [61].

CONCLUSION

Among the various diseases caused by aging, diabetes and sarcopenia appear in elderly people. Reduced β cell function in elderly people lowers insulin sensitivity, which affects protein synthesis and

Table 2 Resistance exercise and sarcopenia

Ref.	Study population and intervention	Study outcome
Zhao <i>et al</i> [58], 2022	24 elderly patients with T2D and sarcopenia; short-term acute resistance exercise (40 min/d, 3 d at 50% of 1RM)	Decreased blood glucose levels, blood glucose fluctuations and the risk of hypoglycemia
Seo <i>et al</i> [62], 2021	12 elderly females with sarcopenia; 16 wk of resistance training (60 min/d, 3 d/wk at 4-8 on the OMNI scale)	Improved functional fitness and muscle quality
Dong <i>et al</i> [63], 2019	21 elderly patients on maintenance hemodialysis with sarcopenia; 12 wk of resistance exercise (3 d/wk at their own body weight and elastic balls)	Improved physical activity status (maximum grip strength, daily pace, and physical activity level), and Inflammatory factors (IL-6, IL-10, and TNF- α)
Liao <i>et al</i> [64], 2018	56 elderly females with sarcopenia obesity; 12 wk of elastic band resistance training (3 training sessions every week for 12 wk, each training session was performed for 55 min)	Significant beneficial effect on muscle mass, muscle quality, and physical function
Hamaguchi <i>et al</i> [65], 2017	7 elderly females with sarcopenia; 6 wk of progressive power training (2 sessions per week for 6 wk; when the subject was capable of completing all 8 sets, the weight was increased by 380-760 g in the next session)	BMD and knee extensor strength were significantly greater in the training group than in the control group
Vasconcelos <i>et al</i> [66], 2016	14 elderly females with sarcopenia; 10 wk of resistance exercise (60 min/d, 2 d/wk; 1-2 wk at 50% of 1RM, 3-4 wk at 75% of 1RM, 5-6 wk at 40% of new 1RM, and 7-10 wk at 60% of new 1RM)	Knee extensor power was significantly higher in the training group than in the control group
Stoever <i>et al</i> [67], 2018	28 elderly people with sarcopenia obesity; 16 wk of progressive resistance training (2 d/wk, increasing to 80%-85% of maximum strength with 3 sets of 8 to 12 repetitions)	Increase performance in hand-grip strength, gait speed, SPPB score, and modified PPT score

T2D: Type 2 diabetes; IL: Interleukin; TNF: Tumor necrosis factor; SPPB: Short Physical Performance Battery; PPT: Physical performance test.

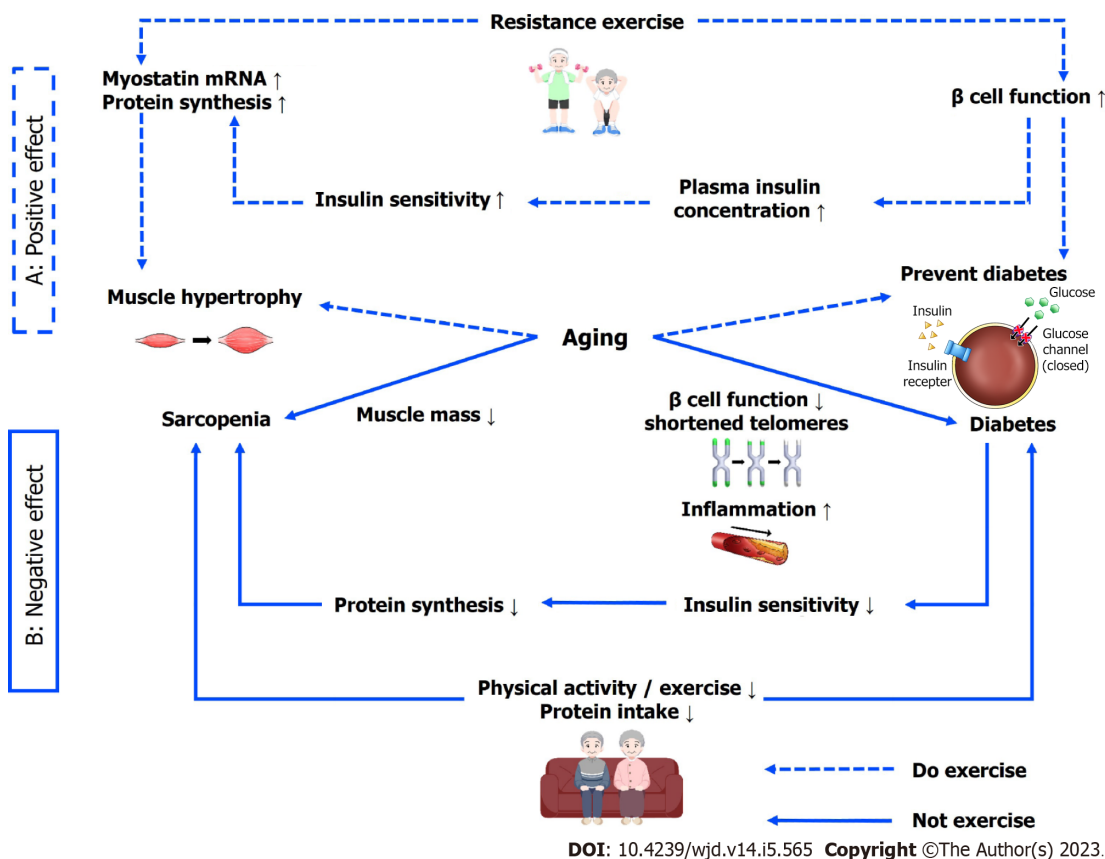


Figure 1 The summary of the factors that cause diabetes and sarcopenia due to the aging and benefits of resistance exercise in the elderly is as follows.

interferes with muscle synthesis. The functional decrease and aggravation of disease in elderly people with less regular exercise or physical activity causes imbalances in food intake and a continuous, vicious cycle. In contrast, resistance exercise increases β cell function and protein synthesis in elderly people. A summary of our conclusions is shown in Figure 1. Regular physical activity and/or resistance exercise

in the elderly is effective in preventing and promoting sarcopenia and diabetes. On the contrary, aging increases the risk of exposure to sarcopenia and diabetes. Therefore, exercise or physical activity should be regularly performed even before aging begins, and muscle mass should be increased through resistance exercise. The protein intake necessary for protein synthesis during resistance exercise should also be maintained in elderly people and those with diabetes or/and sarcopenia.

FOOTNOTES

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Country/Territory of origin: South Korea

ORCID number: Sunghwun Kang 0000-0002-3932-0218.

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