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Contents

Thrice Monthly Volume 9 Number 33 November 26, 2021

REVIEW

- 10052** Effects of alcohol consumption on viral hepatitis B and C
Xu HQ, Wang CG, Zhou Q, Gao YH

MINIREVIEWS

- 10064** Effects of anti-diabetic drugs on sarcopenia: Best treatment options for elderly patients with type 2 diabetes mellitus and sarcopenia
Ma XY, Chen FQ

ORIGINAL ARTICLE

Retrospective Cohort Study

- 10075** Utility of cooling patches to prevent hand-foot syndrome caused by pegylated liposomal doxorubicin in breast cancer patients
Zheng YF, Fu X, Wang XX, Sun XJ, He XD

Retrospective Study

- 10088** Clinicopathological features of small T1 colorectal cancers
Takashina Y, Kudo SE, Ichimasa K, Kouyama Y, Mochizuki K, Akimoto Y, Maeda Y, Mori Y, Misawa M, Ogata N, Kudo T, Hisayuki T, Hayashi T, Wakamura K, Sawada N, Baba T, Ishida F, Yokoyama K, Daita M, Nemoto T, Miyachi H
- 10098** Comparison of dental pulp periodontal therapy and conventional simple periodontal therapy as treatment modalities for severe periodontitis
Li L, Chen HJ, Lian Y, Wang T
- 10106** Tripartite intensive intervention for prevention of rebleeding in elderly patients with hypertensive cerebral hemorrhage
Li CX, Li L, Zhang JF, Zhang QH, Jin XH, Cai GJ
- 10116** Clinical and electroencephalogram characteristics and treatment outcomes in children with benign epilepsy and centrotemporal spikes
Chen RH, Li BF, Wen JH, Zhong CL, Ji MM
- 10126** Endoscopic ultrasonography diagnosis of gastric glomus tumors
Bai B, Mao CS, Li Z, Kuang SL
- 10134** Learning curves of robot-assisted pedicle screw fixations based on the cumulative sum test
Yu J, Zhang Q, Fan MX, Han XG, Liu B, Tian W
- 10143** Value of GRACE and SYNTAX scores for predicting the prognosis of patients with non-ST elevation acute coronary syndrome
Wang XF, Zhao M, Liu F, Sun GR

- 10151** Effectiveness of enhanced recovery after surgery in the perioperative management of patients with bone surgery in China

Zhao LY, Liu XT, Zhao ZL, Gu R, Ni XM, Deng R, Li XY, Gao MJ, Zhu WN

Clinical Trials Study

- 10161** Association between plasma dipeptidyl peptidase-4 levels and cognitive function in perinatal pregnant women with gestational diabetes mellitus

Sana SRGL, Li EY, Deng XJ, Guo L

- 10172** Paricalcitol in hemodialysis patients with secondary hyperparathyroidism and its potential benefits

Chen X, Zhao F, Pan WJ, Di JM, Xie WN, Yuan L, Liu Z

Observational Study

- 10180** Did the severe acute respiratory syndrome-coronavirus 2 pandemic cause an endemic *Clostridium difficile* infection?

Cojocariu C, Girleanu I, Trifan A, Olteanu A, Muzica CM, Huiban L, Chiriac S, Singeap AM, Cuciureanu T, Sfarti C, Stanciu C

- 10189** Effect of nursing intervention based on Maslow's hierarchy of needs in patients with coronary heart disease interventional surgery

Xu JX, Wu LX, Jiang W, Fan GH

- 10198** Impacts of statin and metformin on neuropathy in patients with type 2 diabetes mellitus: Korean Health Insurance data

Min HK, Kim SH, Choi JH, Choi K, Kim HR, Lee SH

META-ANALYSIS

- 10208** Is endoscopic retrograde appendicitis therapy a better modality for acute uncomplicated appendicitis? A systematic review and meta-analysis

Wang Y, Sun CY, Liu J, Chen Y, Bhan C, Tuason JPW, Misra S, Huang YT, Ma SD, Cheng XY, Zhou Q, Gu WC, Wu DD, Chen X

- 10222** Prognostic value of ground glass opacity on computed tomography in pathological stage I pulmonary adenocarcinoma: A meta-analysis

Pan XL, Liao ZL, Yao H, Yan WJ, Wen DY, Wang Y, Li ZL

CASE REPORT

- 10233** Atrial fibrillation and concomitant left subclavian, axillary and brachial artery embolism after fiberoptic bronchoscopy: A case report

Yang CL, Zhou R, Jin ZX, Chen M, Zi BL, Li P, Zhou KH

- 10238** Streptococcal toxic shock syndrome after hemorrhoidectomy: A case report

Lee CY, Lee YJ, Chen CC, Kuo LJ

- 10244** Subsequent placenta accreta after previous mifepristone-induced abortion: A case report

Zhao P, Zhao Y, He J, Bai XX, Chen J

- 10249** Autosomal dominant tubulointerstitial kidney disease with a novel heterozygous missense mutation in the uromodulin gene: A case report
Zhang LL, Lin JR, Zhu TT, Liu Q, Zhang DM, Gan LW, Li Y, Ou ST
- 10257** Novel KDM6A mutation in a Chinese infant with Kabuki syndrome: A case report
Guo HX, Li BW, Hu M, Si SY, Feng K
- 10265** Pancreatic cancer with synchronous liver and colon metastases: A case report
Dong YM, Sun HN, Sun DC, Deng MH, Peng YG, Zhu YY
- 10273** Veno-venous-extracorporeal membrane oxygenation treatment for severe capillary leakage syndrome: A case report
Nong WX, Lv QJ, Lu YS
- 10279** Anticoagulant treatment for pulmonary embolism in patient with cerebral hemorrhage secondary to mechanical thrombectomy: A case report
Chen XT, Zhang Q, Zhou CQ, Han YF, Cao QQ
- 10286** Complete restoration of congenital conductive hearing loss by staged surgery: A case report
Yoo JS, Lee CM, Yang YN, Lee EJ
- 10293** Blastic plasmacytoid dendritic cell neoplasm with skin and bone marrow involvement: Report of three cases
Guo JH, Zhang HW, Wang L, Bai W, Wang JF
- 10300** Extracranial multiorgan metastasis from primary glioblastoma: A case report
Luan XZ, Wang HR, Xiang W, Li SJ, He H, Chen LG, Wang JM, Zhou J
- 10308** Transverse myelitis after infection with varicella zoster virus in patient with normal immunity: A case report
Yun D, Cho SY, Ju W, Seo EH
- 10315** Duodenal ulcer caused by coil wiggle after digital subtraction angiography-guided embolization: A case report
Xu S, Yang SX, Xue ZX, Xu CL, Cai ZZ, Xu CZ
- 10323** Crab lice infestation in unilateral eyelashes and adjacent eyelids: A case report
Tang W, Li QQ
- 10328** Local random flaps for cervical circumferential defect or tracheoesophageal fistula reconstruction after failed gastric pull-up: Two case reports
Zhang Y, Liu Y, Sun Y, Xu M, Wang XL
- 10337** Incurable and refractory spinal cystic echinococcosis: A case report
Zhang T, Ma LH, Liu H, Li SK
- 10345** Individualized treatment of breast cancer with chronic renal failure: A case report and review of literature
Cai JH, Zheng JH, Lin XQ, Lin WX, Zou J, Chen YK, Li ZY, Chen YX

- 10355** Persistent fibrinogen deficiency after snake bite: A case report
Xu MH, Li J, Han L, Chen C
- 10362** Successful prolonged cardiopulmonary resuscitation after intraoperative cardiac arrest due to povidone-iodine allergy: A case report
Xiang BB, Yao YT, Jiao SL
- 10369** Clinical algorithm for preventing missed diagnoses of occult cervical spine instability after acute trauma: A case report
Zhu C, Yang HL, Im GH, Liu LM, Zhou CG, Song YM
- 10374** Carbon ion radiotherapy for synchronous choroidal melanoma and lung cancer: A case report
Zhang YS, Hu TC, Ye YC, Han JH, Li XJ, Zhang YH, Chen WZ, Chai HY, Pan X, Wang X, Yang YL
- 10382** Heart failure as an adverse effect of infliximab for Crohn's disease: A case report and review of the literature
Grillo TG, Almeida LR, Beraldo RF, Marcondes MB, Queiróz DAR, da Silva DL, Quera R, Baima JP, Saad-Hossne R, Sasaki LY

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Effects of anti-diabetic drugs on sarcopenia: Best treatment options for elderly patients with type 2 diabetes mellitus and sarcopenia

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Abstract

Human life expectancy increases as society becomes more developed. This increased life expectancy poses challenges associated with the rapid aging of the population. Sarcopenia, an age-related disease, has become a worldwide health issue. Patients with sarcopenia experience decreases in muscle mass and function, becoming frail and eventually bedridden. Type 2 diabetes mellitus (T2DM) is also a major health issue; the incidence of T2DM increases with aging. T2DM is associated with reduced muscle strength and poor muscle quality and may contribute to acceleration of the aging process, augmenting age-related sarcopenia. Recent studies indicate that elderly patients with diabetes are at an increased risk for sarcopenia. Therefore, these older diabetic patients with sarcopenia need specific anti-diabetic therapies targeting not only glycemic control but also sarcopenia, with the goal of preventing sarcopenia in pre-sarcopenic patients. Presently, various types of hypoglycemic drugs are available, but which hypoglycemic drugs are better suited for geriatric T2DM patients with sarcopenia remains undetermined. In this review, we discuss the association between diabetes and sarcopenia in geriatric patients, and how anti-diabetic drugs may influence sarcopenia outcomes. This review will guide clinical workers in the selection of drugs best suited for this patient population.

Key Words: Type 2 diabetes mellitus; Sarcopenia; Anti-diabetic drugs; Geriatric

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Core Tip: Elderly patients with diabetes are at an increased risk for sarcopenia. Therefore, these older diabetic patients with sarcopenia need specific anti-diabetic therapies targeting not only glycemic control but also sarcopenia, with the goal of

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preventing sarcopenia in pre-sarcopenic patients. We herein discuss the association between diabetes and sarcopenia in geriatric patients, and how anti-diabetic drugs may influence sarcopenia outcomes.

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INTRODUCTION

Diabetes mellitus (DM), a chronic metabolic disease, has reached epidemic status and is considered one of the major threats to human health in the 21st century. In 2017, the International Diabetes Federation estimated that 425 million individuals worldwide have DM; this number is expected to increase to 629 million by 2045[1,2]. Approximately 90% of these individuals have type 2 DM (T2DM)[3], with the highest prevalence of T2DM observed in older adults[4]. Sarcopenia, which, in addition to the traditional microvascular and macrovascular complications, has emerged as a third category of T2DM-associated complications in geriatric individuals with diabetic syndromes, results in considerable disability[5]. Sarcopenia manifests primarily as decreased skeletal muscle mass. Combined with decreased bone mineral content and deteriorating bone quality, sarcopenia causes physical frailty and increases the risk for complications, which decrease quality of life and increase mortality[6]. A progressive decrease in muscle mass occurs at an annual rate of 1%-2% after 30 years of age, accelerates to 1.5%-3% per year after 60 years of age, and progresses even more rapidly after 75 years of age[7]. Because muscle is the main site of glucose consumption, reduced muscle mass leads to increased insulin resistance. Sarcopenia causes insulin resistance, which, in turn, exacerbates the loss of skeletal muscle[8]. Because sarcopenia is multifactorial, the diabetic geriatric population needs specific treatment parameters for both the initial and maintenance therapy using anti-diabetic agents. Therefore, prescribing anti-diabetic agents in such individuals should be conducted to lower not only hyperglycemic levels but also to treat and possibly prevent sarcopenia in pre-sarcopenic patients. In this review, we evaluate the relationship between diabetes and sarcopenia in elderly patients and discuss how certain anti-diabetic agents may play specific roles in influencing disease outcomes.

AGING AND SARCOPENIA

In 1989, Rosenberg first introduced the term “sarcopenia” in reference to age-related loss of skeletal muscle mass and volume[9]. Currently, sarcopenia is defined as an involuntary loss of skeletal muscle and used as predictor of physical disability/mortality. Muscle mass accounts for 75% of body-cell mass and 45% of body mass[10]. Once people reach 60 years of age, they lose 1.5%-3% of their muscle mass per year. Therefore, aging is associated with adverse changes in body composition. Sarcopenia, a common disorder in the elderly, contributes to functional decline, disability, frailty, and falls[11]. Because of the aging of the population, sarcopenia has become a worldwide health concern. In China, the prevalence of sarcopenia in people aged 60 years and older is 10.6% (11.3% in men and 9.8% in women)[12]. In Japan, the prevalence of sarcopenia among community-dwelling older adults aged 65-89 years is 21.8% in men and 22.1% in women[13]. Low muscle mass in the legs is associated with muscle weakness, poor lower-extremity performance, and loss of mobility in older adults[14-16]. In the United States, community-dwelling older adults diagnosed with sarcopenia have a 1.29-fold higher risk for all-cause mortality[17]. The pathogenesis of sarcopenia is poorly understood, although altered hypoxic signaling, oxidative stress, and adipokines may be involved in sarcopenic processes. Age-related, chronic, low-grade inflammation has also been recognized as an important causative factor in sarcopenia[18].

AGING AND T2DM

T2DM is a heterogeneous, multifactorial, polygenic, endocrine, metabolic, chronic, and age-related disease characterized by obesity, insulin resistance, and hyperglycemia [19]. Aging is characterized by a progressive loss of physiological integrity, leading to impaired function. This deterioration is the primary risk factor for major human pathologies including cancer, cardiovascular disorders, neurodegenerative diseases, and diabetes [20]. Nevertheless, our understanding of how cellular aging contributes to the pathogenesis of diabetes is incomplete, and currently, there are no therapies targeting cellular aging in diabetes. Insulin resistance has been shown to induce the expression of aging markers, suggesting that β -cell aging could accelerate progression toward diabetes [21-23]. Therefore, reversing cellular aging may be a potential approach in novel anti-T2DM therapies.

T2DM AND SARCOPENIA

Although the mechanisms underlying the association between T2DM and sarcopenia are currently unknown, mitochondrial dysfunction, muscle protein degradation, and autophagy may be associated with loss of skeletal muscle mass and strength in patients with diabetes [24]. Sarcopenia contributes to functional impairment, and elderly diabetic patients are two times more likely to develop sarcopenia than those without diabetes [25]. The Health, Aging, and Body Composition Study showed that annual decline in appendicular muscle mass in patients with diabetes is approximately 0.2 kg/year (1%/year), while decline in appendicular lean mass in non-diabetic persons is 0.15 kg/year (0.7%/year) [26]. A recent prospective study showed that poor glycemic control is associated with sarcopenia and that chronic inflammation combined with mitochondrial dysfunction and oxidative stress play important roles in muscle atrophy [27]. Interactions among these factors may involve several intracellular signaling pathways that affect the balance between protein synthesis and degradation and induction of apoptosis; these two aspects are involved in the primary pathology of significant muscle mass loss [28].

AGING, T2DM, AND SARCOPENIA

Sarcopenia, one of the most serious health-related problems among elderly adults with diabetes, impairs the activities of daily living, increasing the risk of mortality [29]. Recent studies have reported that elderly patients with diabetes are at an increased risk for sarcopenia [24,26]. Additionally, microinflammation and insulin resistance may be central in the sarcopenia pathogenesis [24]. Previous research has shown that older adults with T2DM have an accelerated loss of muscle mass and strength compared with those of adults without diabetes [26]. Diabetes, which is associated with reduced muscle strength and poor muscle quality, involves an accelerated aging process that intensifies age-related sarcopenia [30]. The results from the Korean Sarcopenic Obesity Study showed that the prevalence of sarcopenia in patients with diabetes is considerably higher than in non-diabetic individuals. In patients older than 60 years, individuals with and without diabetes demonstrated a significant difference in the prevalence of sarcopenia; this was observed for both sexes [9] and agreed with findings obtained in another study [31]. In the general population, studies have shown that with aging, men lose more skeletal muscle mass than do women, even though men have a higher starting skeletal muscle mass compared with that of women [32]; however, women with diabetes are at a particularly high risk for the loss of skeletal muscle mass [26]. The relationship among aging, T2DM, and sarcopenia is illustrated in Figure 1.

ANTI-DIABETIC DRUGS AND SARCOPENIA

Evaluating the use of anti-diabetic agents in older T2DM patients with sarcopenia is important in order to determine which anti-diabetic drugs may alleviate sarcopenia or pose a decreased risk for the progression of sarcopenia. Currently available anti-diabetic agents include biguanides (metformin), insulin secretagogues (sulfonylureas and glinides), alpha-glucosidase inhibitors, thiazolidinediones, dipeptidyl peptidase 4 (DPP4) inhibitors, glucagon-like peptide-1 receptor agonists (GLP-1RA), sodium-

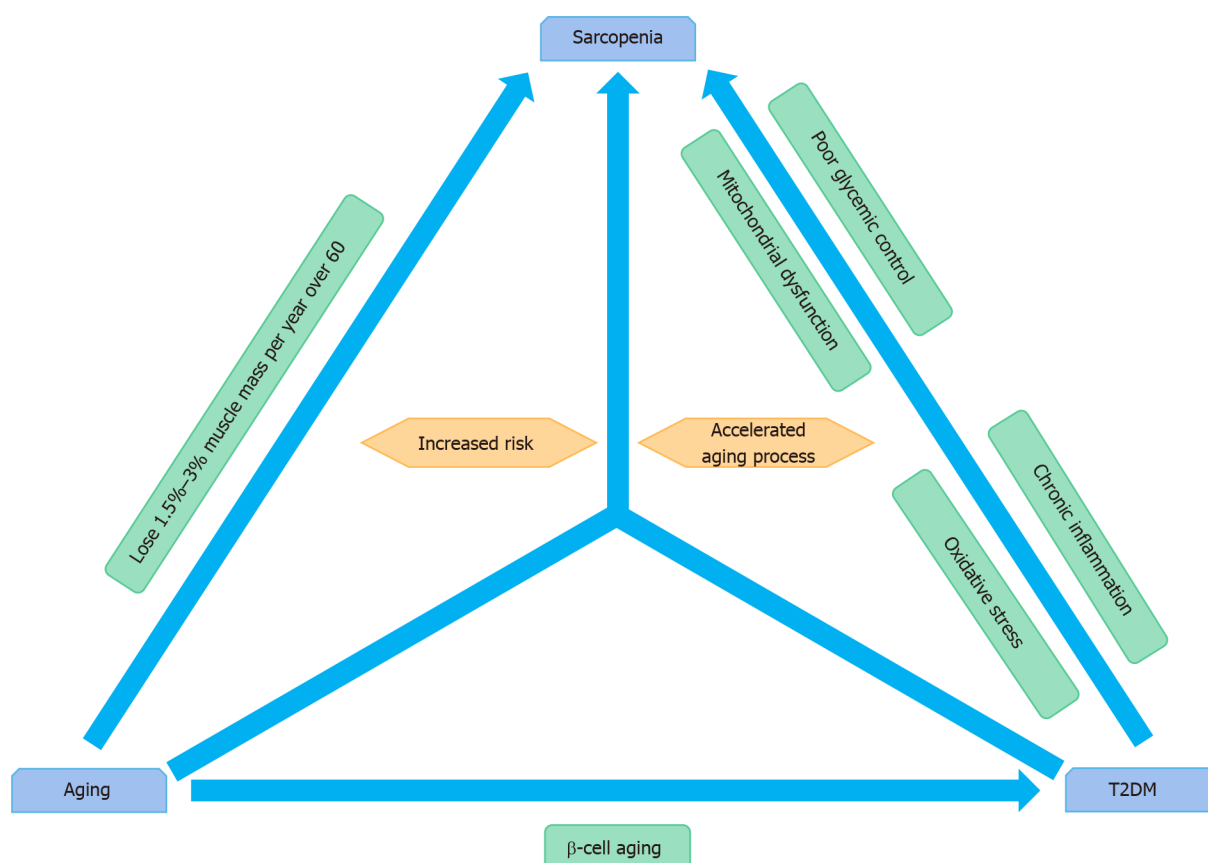


Figure 1 Relationship among aging, type 2 diabetes mellitus, and sarcopenia. T2DM: Type 2 diabetes mellitus.

glucose cotransporter-2 inhibitor (SGLT2i), and insulin. While all of these agents have shown beneficial hypoglycemic effects, we will discuss their potential utility in geriatric patients with sarcopenia (Table 1).

Biguanides and sarcopenia

Metformin (1,1-dimethylbiguanide hydrochloride) lowers blood glucose levels by sensitizing the liver to the effects of insulin, thereby suppressing hepatic glucose output. According to updated guidelines, metformin is considered a first-line treatment for T2DM, especially in elderly diabetic patients. In a study conducted in Iran, 51 individuals newly diagnosed with T2DM (21 men and 30 women) were treated using 1000 mg metformin twice daily for 6 mo; 41 participants (80.4%) completed the study. The results obtained in that study indicated that by week 24, the lean-to-fat ratio increased in the participants, with men showing significantly greater changes compared with those of women. The administration of metformin for 3 mo showed favorable effects on body composition, insulin sensitivity, and glucose homeostasis. This finding suggests that a metformin-based therapy may postpone the development of sarcopenia and may be particularly effective in women with T2DM, who are at an increased risk for the loss of skeletal muscle mass[31]. A two-site, randomized, double-blind, placebo-controlled clinical trial investigating the effects of metformin, combined with a progressive resistance-training program, showed that individuals aged 65 and older, treated using 1700 mg metformin per day for 16 wk, showed increased muscle hypertrophy and strength gains, thereby maintaining functional independence[33]. Another study showed that participants with risk factors for T2DM, treated using 850 mg metformin twice a day for 2 mo, showed a decrease in fat weight and increase in lean weight[34]. In the osteoporotic fractures in men study, 151 diabetic men were treated with insulin sensitizers, and 111 diabetic men were treated without insulin sensitizers, with a follow-up of 3.5 ± 0.7 years. Analysis of specific insulin sensitizers revealed that diabetic men treated using metformin, or using metformin coupled with thiazolidinediones, had significantly reduced total and appendicular lean mass loss compared with that of men with untreated diabetes, or that of diabetic men treated without insulin sensitizers[35]. Metformin increases the activity of adenosine monophosphate-activated protein kinase, which inhibits the

Table 1 Effects of anti-diabetic drugs on patients with geriatric type 2 diabetes mellitus and sarcopenia

Anti-diabetic drugs	Effect on sarcopenia	Good option or poor option
Biguanides	Positive[31,33-36,38-40]/negative[41-44]	Unclear
Insulin secretagogues	Negative[46-48]	Poor
-Glucosidase inhibitors	No data	No data
Thiazolidinediones	Positive[35,53-56]	Careful use
Dipeptidyl peptidase IV inhibitors	Positive[57-60]/neutral[62]	Good
Glucagon-like peptide-1 receptor agonists	Positive[63,70,71]/negative[62]	Unclear
Sodium-glucose cotransporter-2 inhibitor	Positive[72,73]/unclear[6,74]	Unclear
Insulin	Positive/unclear[75]	Unclear

mechanistic target of rapamycin (mTOR)[36], a key factor in muscle growth[37]. Notably, metformin is currently being evaluated in clinical trials for the improvement of muscle function in patients with Duchenne muscular dystrophy[38,39].

Metformin-mediated mechanisms are also being evaluated in animal models. One study has shown that the percentage of centronucleated myofibers in metformin-treated mice is lower than that in control mice at 4 d post-injury. Moreover, at 7 d post-injury, control myofibers show a larger cross-sectional area (500 ha²) than that obtained from metformin-conditioned mice. These data suggest that metformin-treated mice were fully regenerated at 7 d post-injury, indicating that metformin may be used for the maintenance of muscle stem cells during repeated regeneration cycles in disease and aging[40]. However, other studies have suggested that metformin is ineffective in the recovery of muscle mass and strength[41-44]. One study evaluated aged (23 mo) and young (3 mo) male mice fed a low-fat diet without or with the addition of 0.5% metformin for up to 8 wk. The results of that study showed that in aged mice, long-term treatment with metformin does not alter the decreased relative muscle mass that exhibits hyperactive mTORC1 signaling during the fasted state. However, the same treatment paradigm using metformin reduced fasted muscle mTORC1 signaling in young mouse muscle[41]. Consistent with the results obtained in this study, another study demonstrated that 0.5% metformin administered for 6 wk shows limited effects on restoring normal metabolic and growth signaling in aged adipose tissue and muscle, respectively[42]. Other studies have suggested that metformin may negatively impact the mitochondrial function in skeletal muscle[43,44]. Thus, it is unclear whether metformin exerts positive, negative, or negligible effects on muscle mass and strength.

Insulin secretagogues (sulfonylureas and glinides) and sarcopenia

Sulfonylureas are insulin secretagogues that are typically divided into first- and second-generation drugs. Glinides possess a mechanism-of-action that is similar to that of sulfonylureas, but act in a plasma-glucose concentration-dependent manner with a shorter circulating half-life than that of sulfonylureas. Sulfonylureas and glinides, which are ATP-sensitive potassium channel blockers, stimulate insulin release from pancreatic beta cells[45]. Several studies have shown that drugs in this class may be associated with muscle atrophy because they induce a muscle type-dependent atrophy in mice[46]. Additionally, from October 6, 2011 through June 29, 2012, the Food and Drug Administration Adverse Event Reporting System received 1697582 reports of adverse events in human patients. Muscle atrophy was reported in 0.27% of reports on glibenclamide/glyburide. A data-mining analysis, performed by calculating the proportional reporting ratio, revealed a significant association between muscle atrophic events and the use of glyburide[46]. This may occur because hypoglycemia can induce “*in vitro*” apoptosis and autophagic cell death, and high rates of hypoglycemia characterizing glibenclamide use are a precipitating factor in inducing atrophy “*in vivo*” in human patients[47,48]. These findings indicate that insulin secretagogues should not be used as first-line therapy in older T2DM patients with sarcopenia.

Alpha-glucosidase inhibitors and sarcopenia

Alpha-glucosidase inhibitors are known to lower postprandial glucose by inhibiting the breakdown of complex carbohydrates in the intestine. However, at present, no studies have been used to examine the relationship between alpha-glucosidase

inhibitors and sarcopenia.

Thiazolidinediones and sarcopenia

Thiazolidinediones (pioglitazone and rosiglitazone) can improve insulin sensitivity by enhancing insulin-mediated glucose disposal *via* activation of peroxisome proliferator-activated receptor gamma. In 2010, the European Medicines Agency suspended the use of rosiglitazone because of cardiotoxicity; thus, it is not commonly used in China, especially in elderly patients. Recent studies have shown that insulin resistance and mitochondrial dysfunction play an important role in loss of muscle mass[49]. T2DM [50,51] and aging-related sarcopenia[52] are characterized by fatty muscle. One study [53] showed that human satellite cells possess adipogenic potential, which may explain the origin of mature adipocytes within myofibers or within the intermuscular space. Treatment with rosiglitazone does not induce fat conversion in human satellite cells but does considerably enhance the adipogenic potential of these cells, which is triggered by the addition of a specific medium permissive of adipogenesis. Thus, thiazolidinediones, which can increase fatty acid disposal and oxidation in skeletal muscle[54], can reduce increases in intramyocellular triglyceride content and prevent the development of fat cells within muscle fibers[53]. Several studies have shown that peroxisome proliferator-activated receptor gamma agonists exert beneficial effects on muscle performance in older diabetic patients[35,55,56]. However, elderly individuals may have numerous common conditions affecting their health, complicated by coronary heart disease and cardiac insufficiency; thus, prescribing these types of drugs to elderly patients should be undertaken with caution.

DPP4 inhibitors and sarcopenia

DPP4 inhibitors, which are second-line treatment for T2DM, are widely employed because of their safety and effectiveness in glycemic control. Rizzo *et al*[57] reported in a cross-sectional study that elderly diabetic patients treated with DPP4 inhibitors show low levels of inflammatory parameters, high GLP-1 activity during the postprandial state, and high skeletal muscle mass (SMM) and strength compared with those of patients treated with sulfonylurea[57]. Another study showed that changes in the skeletal muscle index (SMI) of patients treated and not treated using DPP4 inhibitors were 0.04 ± 0.03 and -0.12 ± 0.03 , respectively, and that this difference was clinically significant[58]. The findings obtained in this study indicate that DPP4 inhibitors can protect against the loss of muscle mass in Japanese patients with T2DM. Moreover, these 20 patients (11 men and 9 women) with DPP4 inhibitors coupled with sitagliptin for 24 wk significantly reduced total body-fat mass (FM) but not fat-free mass (FFM) [59]. Numerous factors may account for this protective effect. The soluble form of DPP4 induces inflammation, and inflammation can be prevented by DPP4 inhibition [60], which is the presumed cause of sarcopenia[61]. Also, inhibitors of DPP4, a GLP-1 degradation enzyme, are associated with alleviation in the reduction of muscle mass in diabetic and elderly diabetic patients[57,58]. However, another study showed that neither FM nor SMM changed following a 6-mo treatment with teneligliptin in 21 T2DM patients on hemodialysis[62]. Therefore, the effect of DPP4 inhibition on sarcopenia is likely protective or neutral, indicating that DPP4 inhibitors are safe to use in elderly T2DM patients with sarcopenia.

GLP-1RA and sarcopenia

GLP-1 is a 30-amino acid peptide incretin hormone synthesized and secreted by intestinal endocrine L-cells in the small intestine in response to eating. GLP-1 performs numerous physiological actions *via* its receptor, GLP-1R[63]; these actions include promoting glucose-induced insulin secretion, increasing β -cell survival, inhibiting glucagon production, delaying gastric emptying, and regulating appetite[63]. GLP-1R expression in muscle tissues and cells is controversial[64]. GLP-1 can also induce insulin-independent vasodilation and may stimulate nitric oxide synthase phosphorylation in endothelial cells[65]. GLP-1RA may exert anti-sarcopenic effects. A previous study has shown that the GLP-1RA, Ex-4, attenuates muscle atrophy in dexamethasone-induced mouse model of muscle atrophy and in chronic renal disease-derived model of muscle atrophy. Additionally, a long-acting GLP-1RA, dulaglutide, shows a therapeutic effect in DBA/2J-mdx mice, which are used to model Duchenne muscular dystrophy[63].

GLP-1RA have revolutionized the management of T2DM in elderly adults with T2DM who tend to develop sarcopenia and frailty as a result of poor energy intake. Increases in GLP-1 expression may represent a compensatory response to FFM loss, intended to enhance vascular/metabolic coupling in muscle *via* synergistic effect on

nitric oxide and insulin signaling pathways. GLP-1 expression is the strongest predictor of FFM loss, as was shown using the multivariate model[63]. This finding indicates that targeting GLP-1 may potentially be used to reduce FFM loss under hypoxic conditions. This can be achieved using DPP-4 inhibitors or GLP-1RA such as exendin-4; this pharmacological approach is now commonly used in the treatment of diabetes[66]. Inflammation can induce muscle atrophy by regulating the nuclear factor kappa B signaling pathway[67,68], while suppression of inflammation reverses muscle atrophy[68,69]. Indeed, GLP-1RA have shown anti-inflammatory effects in numerous different diseases that involve inflammation[70]. A 24-wk treatment using 3.0 mg liraglutide in overweight and obese elderly patients with T2DM was shown as safe, and none of the patients receiving this treatment became sarcopenic[71]. Unexpectedly, 5 patients showed an improvement in SMI, which was mainly due to an increase in fat-free mass of the legs and arms. Liraglutide reduces body weight and shows particular efficaciousness in reducing fat mass while supporting the stability of trophic SMM. This observation suggests that liraglutide affects muscle by preventing the breakdown of muscle proteins[71]. In another study, however, 6-mo treatment using dulaglutide combined with insulin therapy in T2DM patients on hemodialysis significantly reduced FM and SMM but did achieve significantly improved glycemic control and decreased the insulin dose. Therefore, dulaglutide should be used with caution in these patients because it may promote sarcopenia[62]. In conclusion, it is unclear whether GLP-1RA exert positive or negative effects on muscle mass and strength in patients with T2DM.

SGLT2i and sarcopenia

SGLT2i is a new type of anti-diabetic drug for the treatment of individuals with T2DM. Because of its protective effects on the cardiovascular system and kidneys, it is currently widely prescribed in this patient population. In a previous study, the effects of SGLT2i luseogliflozin on muscle atrophy were investigated in Db/Db mice using cross-sectional areas of the soleus and plantaris muscles. After 8 wk of treatment with luseogliflozin, the cross-sectional areas of the soleus muscle obtained from Db/Db mice not treated with SGLT-2i were significantly smaller than those obtained from Db/Db mice that were treated with SGLT-2i. This may have occurred because of suppression of increased foxo1 expression, which is associated with muscle atrophy in the skeletal muscle of Db/Db mice[72]. However, SGLT-2i shows the opposite effects in humans. A study conducted in Japan showed that the SMI of 37 obese T2DM patients treated with SGLT2 (tofogliflozin) was significantly reduced in both men and women. Although skeletal muscle was significantly decreased, SMI, assessed after such reductions, was sufficiently high and far enough from the cutoff values used in the Asian criteria for sarcopenia[73]. Another report from Japan showed that in T2DM patients treated with luseogliflozin for 52 wk, SMI decreased over the course of the treatment; these changes, however, did not reach the level of statistical significance[6]. These two studies included young obese patients, suggesting that it may not be advantageous to administer SGLT2 inhibitors to older T2DM patients at risk for sarcopenia. SGLT2i should also be used with caution in elderly adults with diabetes because these drugs can increase the risk for both dehydration and sarcopenia[74]. Currently, it is unclear whether SGLT2i exert positive or negative effects on sarcopenia. Further investigations are required in order to maintain adequate levels of skeletal muscle mass during treatment with SGLT2-i in T2DM patients.

Insulin and sarcopenia

Insulin, a powerful anabolic signal in proteins, may prevent sarcopenia in patients with T2DM. Insulin is known to stimulate muscle-protein synthesis in young adults, but not in older individuals or animals[75]. However, the beneficial effects of insulin on sarcopenia have not been yet confirmed in clinical settings.

Anti-diabetic drugs and resistance exercise also exert beneficial effects in T2DM patients with sarcopenia. One study assessed the effects of modified plant-based Mediterranean diet, circuit resistance training, and empagliflozin, separately and in combination, on the body composition and physical function of older individuals with T2DM. The results of that study showed that these interventions were effective in delaying the progression from diabetes to sarcopenia and/or frailty[76]. Another study showed that a combined exercise-metformin intervention therapy benefitted older individuals by promoting muscle hypertrophy and strength gains, thereby maintaining functional independence[33].

CONCLUSION

Sarcopenia is an increasingly common problem in the elderly, especially in geriatric patients with T2DM and in those receiving treatment with anti-diabetic agents. Therefore, it is important to assess appropriately a patient's condition before administering anti-diabetic drugs. Elderly patients are at a much higher risk than younger patients for the side effects of anti-diabetic drugs. This review will aid clinicians in their selection of appropriate anti-diabetic drugs for the treatment of geriatric T2DM patients with, or at risk for, sarcopenia.

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