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Review

# Diabetes and Sarcopenia: Intersection of Co Morbid Conditions

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**Abstract**

Sarcopenia is more common in persons with type 2 diabetes mellitus (T2DM) than in persons without diabetes. There is overlap of some pathophysiologic features of sarcopenia and T2DM. In addition, the risk for sarcopenia is associated with common complications of T2DM including renal disease, cardiovascular disease and neuropathy. Glycemic control in T2DM may have some benefits on sarcopenia. The specific effects of glucose lowering agents on sarcopenia suggest that metformin, insulin, thiazolidinediones and GLP1 receptor agonists may have favorable effects on sarcopenia while SGLT2 inhibitors may have an adverse effect. However, GLP1 RA's and SGLT2 inhibitors have been associated with favorable effects on cardiovascular and renal outcomes and thiazolidinediones with an increased risk for heart failure. Thus glucose lowering risk/benefit ratio overall is key to selection of glucose lowering agents. Nutrition guidelines for T2DM generally align with recommendations for sarcopenia. Data on the benefits of aerobic and resistance exercise in patients with T2DM and sarcopenia is very limited, but some data suggest a benefit of resistance exercises.

**Keywords**

Type 2 diabetes mellitus; sarcopenia; diabetes complications

## 1. Introduction

This article will focus on the intersection of type 2 diabetes mellitus (T2DM) and sarcopenia. The content will include overviews of the data on the incidence of each disorder, how T2DM and sarcopenia are diagnosed and a brief discussion of overlap of some of the mechanisms common to each disorder. This discussion will be followed by studies on the incidence of sarcopenia in diabetes as well as the relationship of comorbidities of diabetes including renal disease, cardiovascular disease and neuropathy and associated sarcopenia risk. Finally, there will be a review of considerations about potential effects of glucose lowering and glucose lowering medications on sarcopenia as well as information on the effects of lifestyle interventions in T2DM and Sarcopenia. Comprehensive reviews have broadly captured many of the issues on sarcopenia and diabetes [1]. The current manuscript is designed to give the reader a general sense of the relationships between these two disorders based on data and details from selected relevant publications.

## 2. T2DM Incidence and Complications

T2DM is a disease that affects 462 million persons worldwide (6.2% of the population) [2]. Common variables associated with increased risk for diabetes include increasing age and obesity. Age related incidence is 4.4% of those aged 15-49 years, 15% of those aged 50-69, and 22% of those aged 70+. T2DM doubles the risk for atherosclerotic vascular disease. The microvascular complications of T2DM are also increased. T2DM is a leading cause of end stage renal disease, of blindness due to diabetic retinopathy and of lower extremity amputations associated with peripheral neuropathy (and often associated with peripheral vascular disease). The relationship of sarcopenia with increasing age parallels the observation of increasing T2DM with age. The interface between T2DM and its comorbidities with sarcopenia is the focus of this paper.

## 3. Sarcopenia Definition and Incidence

Sarcopenia is generally defined by a progressive and accelerated loss of skeletal muscle mass resulting in loss of strength and declining physical function [3-5]. The associated physical disability is greater than that associated with normal aging. Sarcopenia is thus associated with a reduction in the quality of life and frailty. While there is no single clear definition of sarcopenia, the reported prevalence range by Petermann-Rocha et al. for overall sarcopenia at age 60 is 8-36% and for severe sarcopenia is 2-9% [6]. Morley et al. using the related concept of frailty and noting that sarcopenia was a major contributor to frailty reported the following: “A recent systematic review incorporating 31 studies of frailty in persons 65 years or older found a prevalence of from 4.0% to 17.0% (mean 9.9%) of physical frailty, with a higher prevalence when psychosocial frailty was also included. Women (9.6%) were almost twice as likely as men (5.2%) to be frail. The prevalence of frailty is markedly increased in persons older than 80” [7]. The absence of a specific biomarker comparable to glucose for diabetes means that relationships with other disease state such as diabetes are mostly by association [8]. Finally, in contrast to T2DM, there is no specific pharmacotherapy for sarcopenia [5, 8]. Thus assessing any generally approved specific pharmacotherapy for sarcopenia is not currently possible.

## 4. Characterization of Diabetes Mellitus

Diabetes mellitus is a syndrome defined by the presence of hyperglycemia [9, 10]. The level of hyperglycemia to define diabetes mellitus has changed over time, but currently is defined by fasting glucose concentrations ≥126 mg/dl (53 mmol/mol) or by HbA1c of ≥6.5% (≥7 mmol/L). Diabetes mellitus has been further classified into "types" with type 1 diabetes and T2DM being the most commons forms of diabetes [10, 11]. Type 1 diabetes is an autoimmune disorder in which there is a progressive decline of beta cell function mediated by antibodies directed at the beta cell. Sarcopenia is infrequent in type 1 DM and will not be discussed. T2DM is characterized by pathophysiologic processes including insulin resistance and beta cell dysfunction which have been studied over several decades. Other pathophysiological abnormalities related to insulin production and action as well as inflammation and mitochondrial dysfunction have also been described [12, 13]. T2DM is known to have a genetic predisposition (based on identical twin studies and the Human Genome Project). Multiple genes have been associated with T2DM, only the autosomal dominant forms have been well defined genetically. Finally there are secondary types of diabetes associated with glucocorticoid excess, abnormalities in iron metabolism and lipodystrophic disorders. These specific forms of T2DM will not be discussed in terms of possible relationships to sarcopenia. The focus of this report will be derived from studies of T2DM or general studies in persons without diabetes in which the results may be relevant to diabetes.

Comorbid conditions associated withT2DM include obesity, dyslipidemia, hypertension (the "metabolic syndrome") which are, in turn, associated with increased risks for renal disease, cardiovascular disease, and peripheral neuropathy in T2DM. These comorbid disorders have relationships with sarcopenia, and these relationships will be discussed below. Hyperglycemia and management strategies to control hyperglycemia including both life style and pharmacologic agents and their associations with sarcopenia and are discussed in the final sections.

## 5. Characterization of Sarcopenia

Several expert groups have provided definitions of sarcopenia which generally include measures of muscle mass, muscle strength (especially hand grip, ability to get up) and muscle function (timed walking distance and ability to get up from seating/walk/return to seating) as well as impedance and radiographic measures [14]. Among the most widely used criteria are the European Working Group of Sarcopenia in Older People (EWGSOP) [15, 16], the Asian Working Group for Sarcopenia (AWGS) [17, 18], an international working group [19] and the National Institutes of Health (NIH) project [20]. There have been comparisons some of these measures highlighting differences in definitions of sarcopenia with suggestions that criteria may be study cohort specific [21]. In addition, a consortium of experts performed analyses of multiple studies to determine which measures of sarcopenia were associated with significant outcomes [22]. Key conclusions were that both low grip strength and low usual gait speed independently predicted falls, self-reported mobility limitation, hip fractures, and mortality in older adults. In the current article, various criteria to define sarcopenia have been used in the reported studies. Differences in the diagnostic criteria used for sarcopenia do not affect the main messages of relationships between T2DM and sarcopenia.

## 6. Proposed Mechanisms for T2DM, Sarcopenia and Potential Areas of Overlap

The mechanisms underlying the risk for T2DM are complex and evolving. Both insulin resistance and declining beta cell function are well-established mechanisms for hyperglycemia. However, over time additional mechanistic studies have defined other mechanisms that contribute to hyperglycemia [12]. In addition, both Inflammation and mitochondrial dysfunction are also associated with T2DM, especially in the face of kidney disease [23-26]. Inflammation and mitochondrial dysfunction and other features of T2DM have also been associated with sarcopenia [27-29]. Whether there is overlap between inflammation and mitochondrial dysfunction in diabetes and sarcopenia has not been definitively characterized. A simple schematic of possible relationships is shown in Figure 1. Detailed discussion of possible physiological and metabolic relationships between T2DM and sarcopenia are beyond the scope of this paper, however, recognition of the potential for such relationships needs to be acknowledged and several authors have provided detailed discussions and figures with potential mechanistic relationships between T2DM and sarcopenia [27, 28, 30-32].

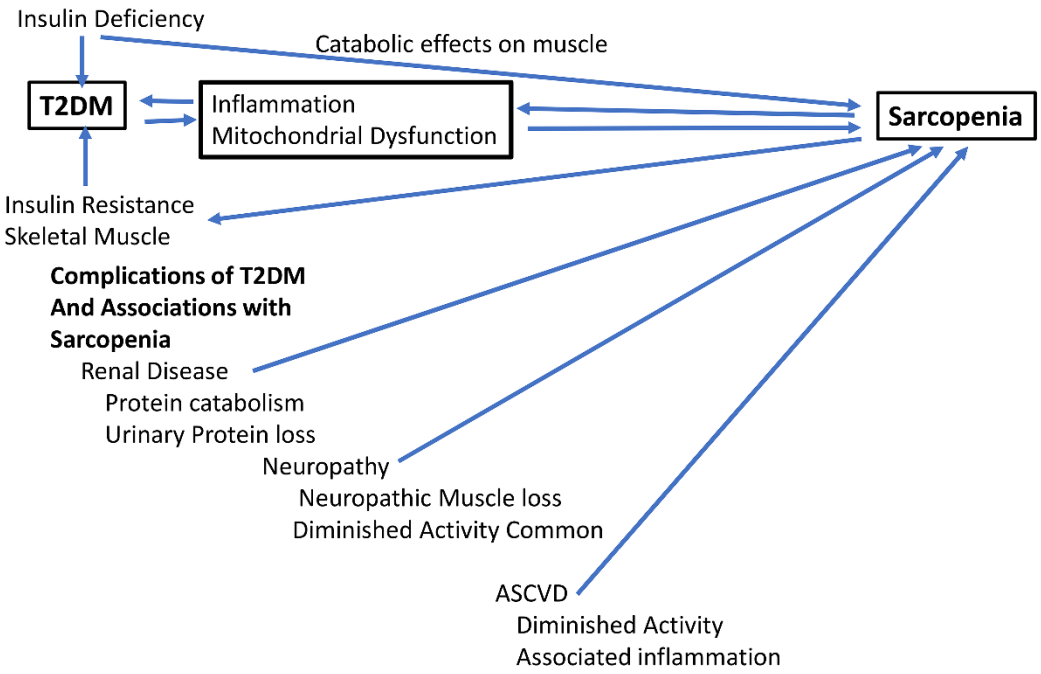


**Figure 1** Summary of Potential Mechanistic Relationships Among Type 2 Diabetes Mellitus, Complications of Diabetes Mellitus and Sarcopenia. See [27, 28, 30-32] for some detailed schematics.

## 7. Risk for Sarcopenia in T2DM

There are several data sets that demonstrate that sarcopenia is more common in T2DM compared to non-DM cohorts [33-37]. Anagostis and colleagues performed a systematic review of 24 cross-sectional and observational studies including 6526 participants from which there were 1832 patients with T2DM, 4694 euglycemic subjects and 1159 cases of sarcopenia defined variably by EWGSOP/AWGS/FNIH criteria [33]. Analyses using data from 15 of the studies showed a 55% increased risk for sarcopenia with DM compared to normoglycemic subjects (OR 1.55, 95% CI 1.25–

1.91, p < 0.001). Similar results were reported by Veronese et al. whose comparison of 10 reported cohorts showed a greater than 60% risk for sarcopenia in T2DM than without DM (OR: 1.635 [95% CI 1.204–2.220; *p* = 0.002]) [34]. Izzo and colleagues reviewed 22 studies published between 2000 and 2020 and reported that the sarcopenia prevalence in DM was between 7.2% and 29.3% in these studies [35]. Ai's review of 28 studies also showed an increased risk of sarcopenia in diabetes and also showed associated risks with increasing age, chronic hyperglycemia and male gender [36]. Finally, Dai et al. analyzed a representative cohort of adults in the United States from the NHANES [37]. In more than 6,000 adults including more than 1400 persons with diabetes, sarcopenia prevalence was 17.5% in the diabetes cohort and 15.7% in the non-diabetes cohort (37% increase with diabetes). The Dai data support the other observations that sarcopenia in DM patients is higher than in non DM and also with increasing age and decreased physical activity.

In summary, sarcopenia is more common in T2DM than in non-DM patients and aging, hyperglycemia, lower BMI and reduced physical activity in T2DM are associated with even greater risk for sarcopenia.

## 8. Risk for Sarcopenia in T2DM with Comorbid Conditions (Table 1)

**Table 1** Risks of Sarcopenia in T2DM (A) and Increased Risk of Complications in T2DM with Sarcopenia (B).

| T2DM Descriptor | Percentage increased risk | References | Comments |
|---|---|---|---|
| A. Risk of Sarcopenia in T2DM | >50% | [33-37] | Diabetes associated with increased prevalence of sarcopenia. Prevalence of sarcopenia in DM increases with increasing age, hyperglycemia (chronic) and lower BMI |
| B. Risk of T2DM Complications with Sarcopenia | | | |
| Renal Disease in Diabetes | | [36, 38-44] | |
| Albuminuria | >200% | [44-47] | |
| Decreased eGFR | >300% | [46, 48] | Note: Catabolic pattern of protein turn over in T2DM |
| Risk of Cardiovascular Disease in Patients with Sarcopenia | | | |
| CVD | >70% | [22, 49, 50] | |
| Stroke | >80% | [49] | |
| HF | >200% | [49] | |
| Mortality | >200% | [50] | |
| Neuropathy in Diabetes | >200% | [51-59] | |

T2DM is associated with a significantly increased risk for renal disease and cardiovascular disease attributable both to the presence of hyperglycemia and the commonly associated risk factors of obesity, dyslipidemia and hypertension [60]. Selected studies of the association of sarcopenia with renal disease, cardiovascular disease and neuropathy will be discussed in turn.

### *8.1 Renal Disease*

Because end stage renal disease, especially when patients are on dialysis, is associated with loss of muscle mass, the relationship between renal disease and sarcopenia has been studied by several groups [36, 38-44]. Decreased muscle mass and diminished strength are commonly observed in such patients. However, observations of sarcopenia with earlier stages of renal disease are also noteworthy. Ida et al. performed a meta-analysis and systemic review of observational studies evaluating the relationships of albuminuria and estimated glomerular filtrations rate (eGFR) and the presence of sarcopenia [46]. Albuminuria is a marker of renal disease even before there may be a decline in renal function as measured eGFR. In Ida's report, albuminuria was associated with a greater than 2 fold increase in measures of sarcopenia [46]. The observation of a relationship between sarcopenia and albuminuria was also reported from a Korean National Health and Nutrition Survey with similar magnitude of risk [45]. Han et al., reported that the association of albuminuria with sarcopenia was consistent in older patients, but not as consistent in younger patients [45]. Zanetti et al. performed an evaluation of protein turnover in a small number of patients with T2DM with and without albuminuria [44]. Using turnover of the essential amino acid phenylalanine, they concluded that T2DM patients with increased urinary albumin "exhibit a catabolic pattern of whole body protein turnover." These observations may provide some insights into the mechanisms between sarcopenia and albuminuria in T2DM.

Declining eGFR is also a marker of renal disease, and the association of lower eGFR with sarcopenia has also been reported. Ida reported there was a 3 to 4 fold increase in sarcopenia with declining eGFR (OR 3.75 95% CI 1.24–11.41 [46]). Similar relationships between albuminuria and declining eGFR with sarcopenia have been reported in other data sets [47, 48]. Any relationship between eGFR and sarcopenia is confounded by the fact that impaired renal function is also associated with a reduction in muscle mass, and a reduction in creatinine excretion as a result of lower muscle mass. Loss of muscle mass affects eGFR calculations. Thus, the association of sarcopenia with declining eGFR is confounded by the loss of muscle mass.

### *8.2 Cardiovascular Disease*

Boonpor et al. used data from the UK Biobank and analyzed the relationships of sarcopenia using the European Working Group on Sarcopenia in Older [16] people definition of sarcopenia in about 12,000 persons with T2DM [49]. The outcomes included CVD, stroke, heart failure and myocardial infarction (MI). Follow up was 10.7 years. When compared to patients without sarcopenia, the patients with sarcopenia had higher levels of deprivation, lower levels of education, were more likely to be smokers and have higher sedentary time and lower levels of physical activity. In models adjusted for age, sex, deprivation index, education, smoking status, alcohol intake, total sedentary time, total physical activity and duration of DM, sarcopenia was associated with a 77% increased risk for CVD (HR: 1.77 [95% CI 1.76-2.37], $P < 0.0001$), 89% for stroke(HR: 1.89 [95% CI 1.36-2.61] $P < 0.0001$), and HF was more than doubled (HR: 2.28 [95% CI 1.86-2.80], $P < 0.0001$). In analyses of MI,

the point estimates for each of three models were >1, but in the fully adjusted model the HR of 1.49 (95% CI 0.99-2.24 P = 0.053) did not achieve statistical significance. When the authors investigated which features of sarcopenia were associated with outcomes, lower grip strength and slow walking pace were associated with higher incidences of each of the cardiovascular outcomes. These data are consistent with the observations of Bhasin et al. on other sarcopenia related outcomes [22]. Song et al. analyzed the relationships among DM, Sarcopenia (SP) and CVD in a cohort from the Korean Health and Nutrition Survey [50]. They compared four groups: DM-/SP-, DM+/SP-, DM-/SP+, and DM+/SP+. When the DM+/SP+ group was compared to the DM-/SP- group, cardiovascular mortality was more than twice as high (HR 2.10; 95%CI 1.11-4.00) while the other two groups had intermediate HRs which did not achieve statistical significance (DM+/SP-: HR 1.39, 95% CI, 0.79-2.30; DM-/SP+: HR 1.42, 95% CI 0.84-2.43).

In summary, these data show a relationship between sarcopenia risk and several measures of atherosclerotic cardiovascular disease.

### *8.3 Neuropathy*

There are many studies on the relationship of neuropathy and the risk for sarcopenia in T2DM. Some of these studies look at general associations of all microvascular complications of diabetes, including neuropathy in the analyses. These articles report general associations between diabetes peripheral neuropathy (DPN) and sarcopenia, but a causal relationship cannot be established [51-59, 61]. The association between DPN and sarcopenia exists even with adjustment for variables such as age, gender, BMI, HbA1c and eGFR [59]. Wannarong et al. performed a meta-analysis of 5 studies which included 4287 participants. Each of the 5 studies had point estimates consistent with an association between DPN and sarcopenia; the pooled analysis found a significant 62% increased risk of sarcopenia with DPN (OR 1.62 [95% CI: 1.30–2.02] $p < 0.0001$). Similarly, Sravya found that the presence of neuropathy was much higher in patients with sarcopenia than those without [56]. Yasmerin reported that sarcopenia incidence in patients who had DN was higher at a significant level than in those without DN (24.7%-8.9%). In the multivariate logistic regression analyses, DPN was determined to be associated with sarcopenia, independently from age and gender, even from accompanying concomitant diseases, BMI, HgA1c and GFR levels (OR: 2.38, 95% CI: 1.02-5.54). In a small Japanese study, reduced walking speed in patients with DM and sarcopenia was only seen with more advanced DPN [52]. Because DPN is associated with a loss of kinesthetic sense, an increased risk for falls has been observed [62-64]. The loss of kinesthetic sense may lead to a fear of weight bearing exercise. Sarcopenia has also been associated with fracture risk [65]. However, no large studies have evaluated whether the combination of DPN and sarcopenia are associated with even a greater risk for falls or fractures. Since DPN and sarcopenia likely have overlapping, but distinct differences in the mechanisms by which falls may occur it is likely that the combination of DPN and sarcopenia would be associated with a predicably higher risk for falls than either by itself. Typical approaches to reducing the risk for falls in elderly patients, especially those with DPN, include measures such as 3 point balance (canes and bathroom bars), avoiding scatter rugs and ensuring adequate lighting, these measures should be maximized in patients with DPN and sarcopenia.

### *8.4 Hyperglycemia, Hyperglycemia Management and Sarcopenia (Table 2)*

**Table 2** Intersection of Hyperglycemia, Glucose Lowering Medications and Lifestyle Interventions in Diabetes and Sarcopenia.

| Risk/Intervention Variable | Comments | References | Additional Comments |
|---|---|---|---|
| Hyperglycemia in Diabetes and Sarcopenia | Hyperglycemia and Aging are Associated with increased risk for both diabetes and Sarcopenia | [66] | This relationship raises the question of causality or reverse causality |
| Glucose Lowering Medications Effects on Sarcopenia | | | |
| General | Likely benefits of improved glycemic control | | There are no robust data from large clinical trials and observational studies are limited; It is difficult to distinguish a benefit from glucose lowering vs a direct benefit of a specific class of medications. This is in contrast to beneficial CVD and renal effects of some medications independent of their glucose lowering effects |
| By Medication Class Overall | | | Data from the metanalyses and systemic reviews are not entirely concordant in proposed medication class effects. |
| Insulin, TZD's, Metformin and perhaps GLP1RAs | Possibly beneficial | [36, 67, 68] | Insulin is an anabolic hormone; TZD's improve insulin resistance (insulin resistance is associated with loss of muscle mass). |
| DPP4 inhibitors, Carbohydrase Inhibitors | Likely Neutral | [67] | |
| Sulfonylureas, SGLT2 inhibitors | Possibly adverse | [68-70] | This possible risk for sarcopenia is balanced by favorable benefits of SGLT2 inhibitors on CVD and renal outcomes |

| | | |
|---|---|---|
| Life Style Interventions | | |
| Nutrition Therapy | Total Energy Intake, Carbohydrate Intake and Protein Intake are Lower in Sarcopenia and Diabetes Associated Sarcopenia | [71] |
| | No Good Intervention Studies to Demonstrate Effects of Nutrition Composition on Sarcopenia in Diabetes | |
| Physical Activity | Observational Data Show a General Relationship Between Reduced Aerobic Activity, Resistance Training and Sedentary Time in Persons with Sarcopenia and in Diabetes with Sarcopenia | [71, 72] |
| | Limited Intervention Data suggest benefits of both aerobic and resistance train on functional improvements in persons with Sarcopenia and Diabetes | [73-75] |

Several studies have shown that, in addition to similar disease mechanisms, age and hyperglycemia are both associated with increased risk for sarcopenia. T2DM is not only increases with aging [2], but hyperglycemia is also associated with increasing duration of disease. These factors confound any causal relationships among increasing age, hyperglycemia, and sarcopenia. The interface between muscle loss and glycemic control also poses a conundrum. Insulin resistance is a function of reduced muscle mass. Loss of muscle mass predisposes to increasing insulin resistance and associated hyperglycemia [12]. Thus any treatment of hyperglycemia and the effects of glycemic control on sarcopenia is confounded by possible reverse causality [13] sarcopenia may result from the presence of hyperglycemia and muscle loss increases insulin resistance causing worsening of hyperglycemia Nevertheless, it is useful to look at glycemic control and approaches to glycemic control on sarcopenia.

Cross-sectional studies of sarcopenia in diabetes suggest a relationship between sarcopenia and glycemic control although this has not been observed in all studies. Alfaro-Alvarado et al. studied 364 patients with DM aged 60 years or older and reported relationships with sarcopenia (using the EWGSOP) definition [15, 66]. In comparisons of 194 patients without sarcopenia with 162 patients with sarcopenia, mean HbA1c values were higher in patients with sarcopenia (8.2% vs. 7.8%, $P = 0.027$) correspondingly more patients with sarcopenia had HbA1c values ≥7.5% (62.3% vs. 47.9%, $P = 0.007$). In addition, patients with sarcopenia were older (77 ± 7.2 vs. 72.6 ± 7.8 yrs, $P < 0.001$) and had longer duration of DM (18.2 ± 9.8 vs. 14.2 ± 9.1 yrs, $P < 0.001$).

### *8.5 Glucose Lowering Agents for T2DM*

Before describing the relationships of glucose lowering agents in sarcopenia, a brief review of mechanisms by which agent lower glucose and a summary of effects on complications is important background information. Historically insulin and sulfonylureas were the most widely used agents. Sulfonylureas stimulate insulin secretion in a non-glucose dependent fashion. Sulfonylurea mediated insulin effects result in weight gain. Glucose lowering with sulfonylureas may reduce microvascular complications of diabetes, but they have no direct effect on the complications. Insulin therapy is similarly associated with weight gain. Glucose lowering with insulin reduces microvascular complications, but has no direct effect on reducing complications. Insulin not only has glucose lowering effects, but is associated with peripheral fat deposition and is generally considered to be anabolic with regard to protein metabolism. Metformin (a biguanide) has also been available for several decades. Metformin reduces hyperglycemia by reducing hepatic glucose production and has some nominal effects on insulin resistance, but has little effect on body weight or muscle mass. The DPP4 inhibitors (gliptins) inhibit the enzyme that degrades native glucagon like peptide 1 (GLP1) DPP4 inhibitors do not have effects on complications beyond glucose lowering effect and are generally weight neutral. GLP1 receptor agonists (GLP1RA) affect glycemic control in a glucose dependent manner and are associated with weight loss. The more potent agents are associated with greater weight loss. This weight loss is associated with both a loss of body fat as well as muscle mass. Because weight loss is generally associated with favorable effects on general physical activity, the independent effects on loss of muscle mass have not been carefully characterized. In addition, there is currently no good data on the most potent GLP1RAs or the more recently approved dual (GLP1/GIP) agonists. These new agents are associated with much greater weight loss (mean reductions of 15% to 24% and lean body mass loss of 10% [76]. However, to date there is no clear data demonstrating

and increased risk for sarcopenia associated loss of muscle mass even in older age groups. GLP1 RAs are associated with a reduction in CVD and renal disease risks. The SGLT2 inhibitors work by interfering with glucose resorption in the kidney especially in the post prandial state. The SGLT2 inhibitors are associated with modest loss of body weight, but generally less than the GLP1RAs. SGLT2 inhibitors are also associated with a reduction in CVD events, renal disease progression and all-cause mortality. The mechanisms by which these benefits occur have been extensively investigated without clear causal associations between glucose lowering, body weight reduction or other pathophysiological mechanisms. The two other agents discussed below, thiazolidinediones (TZDs) and carbohydrase inhibitors are used with decreasing frequency. TZD's are associated with weight gain mostly in the subcutaneous fat and reduced visceral fat. Carbohydrase inhibitors are generally weight neutral. Both of these last two classes of medications have data suggesting some CVD benefit

### *8.6 Effects of Glucose Lowering Agents on Sarcopenia*

The effects of glucose lowering agents on features of sarcopenia is still an evolving story. As noted above common glucose lowering medications in type 2 DM include insulin, a biguanides (mostly metformin), GLP1 receptor agonists, SGLT2 inhibitors, DPP4 inhibitors, as well as less commonly used medications including thiazolidinediones (TZDs) and carbohydrase inhibitors, Massimino et al., have performed one of the more detailed reviews of both the mechanisms of glucose lowering agents and their effects on measures of sarcopenia [68]. Salom Vendrell et al. have provided a thoughtful review of potential mechanisms relating DM and sarcopenia and linked these mechanisms to those of glucose lowering agents in many cases based on the Massimino mechanistic considerations [13]. Based on their analyses of the data in the reviewed studies, Massimino concluded that while there may be beneficial effects directly related to glucose lowering, they propose that there are likely direct effects of the glucose lowering agents themselves. They conclude that insulin is likely beneficial because of its anabolic effects, DPP4 inhibitors are likely neutral for sarcopenia benefit or risk and SGLT2 inhibitors have the potential to have an adverse effect on sarcopenia. Data on other medications are confounded by methodological issues, differences in observational and prospective trial data sets, differences in measures of sarcopenia and small data sets. The most widely used medication in the treatment of T2DM is metformin. Both Ma and Massimino reviews summarizing study data on metformin suggests that it has a neutral to small beneficial effect on functional measures associated with sarcopenia [67, 68]. TZDs may have a beneficial effect on sarcopenia, but their use is waning because of associated heart failure concerns. Sulfonylurea data are confounded by negative effects on sarcopenia in a review of cross-sectional studies and neutral effects in a prospective study [68]. Other small studies also suggest a favorable benefit of GLP1 RA's on sarcopenia [77]. One small observational study in older patients suggested a beneficial effect of a DPP4 inhibitor compared to sulfonylurea. The possible association of worsening sarcopenia with SGLT2 inhibitor use as also been reported in other small studies [69, 70].

Differences between Ma's review of the use of glucose lower agents in older patients with DM and sarcopenia is not entirely aligned with the considerations in Massimino's report [67]. Ma notes that there are likely beneficial effects of biguanides, insulin, DPP4 inhibitors, TZDs, GLP1RA's and SGLT2 inhibitors on sarcopenia, but the use of each class of agents is "unclear" with the exception of the DPP4 inhibitors which is described as a "good" option and TZD's "with careful use." In

guidelines documents the beneficial effects of GLP1 RAs and SGLT2 inhibitors on cardiovascular (including heart failure) and renal disease are important in the selection of glucose lowering agents. The beneficial effects of these two classes of agents have been confirmed by large randomized clinical trials as well as observational data. Thus the effects on CVD and renal disease overshadow sarcopenia concerns in the selection of glucose lowering agents [78].

Management of T2DM needs to be individualized based on patient characteristics and risks. When weight loss, muscle wasting and decreased strength are the primary concerns, current evidence suggests that metformin and insulin are the basis of therapy. If cardiovascular risk is a serious concern, then management of hyperglycemia may include a GLP1RA but with careful attention to any associated weight loss. If both cardiovascular and renal disease are concerns, the addition of an SGLT2 inhibitor may be a consideration, but again with careful consideration for any impact of weight loss on the manifestations of sarcopenia.

## 9. Life Style Variables and Associations with Diabetes Mellitus and Sarcopenia

### *9.1 Lifestyle Interventions: Nutrition Therapy*

There are few intervention studies on lifestyle regimens limited to persons with T2DM and sarcopenia. However, observational data are instructive and intervention data from non-diabetes cohorts are likely applicable to persons with T2DM. Kim et al. reported on nutrient intake, physical activity and biomarkers of sarcopenia in diabetes [71]. They used data from a representative sample of people from the Korea National Health and Nutrition Examination Survey (KNHNES) IV to IV (2008-2010) from 2952 persons ≥65 years old and divided them into 4 categories for analyses: Sarcopenic diabetes (n = 197), Sarcopenia alone (n= 770), Diabetes alone (n = 384) and non-sarcopenia and no diabetes (n = 1601). Total energy intake, carbohydrate intake and protein intake were all lower in sarcopenic diabetes than sarcopenia alone or diabetes alone in men. Total energy intake and carbohydrate intake in both sarcopenic groups were lower than in the non-sarcopenic groups in women, but there were no differences between sarcopenic diabetes and sarcopenia alone. Cross sectional observational studies have demonstrated a relationship between reduced nutrient intake and sarcopenia both in the absence of DM and with DM. Associated biochemical abnormalities included lower hemoglobin and vitamin D levels in the sarcopenic DM patients compared to the other groups. Mesinovic conducted an extensive review of potential therapies for management of sarcopenia and diabetes. In his review of nutritional therapy, the Mediterranean diet has arguably the best supporting data. The American Diabetes Association (ADA) is more circumspect with regard to specific dietary therapy and simply note that “Optimal nutrition and protein intake is recommended for older adults with diabetes.”

There is support for recommending at least 1 gm/kg body weight of protein in the diet in diabetes guidelines. However, recommendations from experts in sarcopenia generally recommend higher levels of protein intake [7, 79-81] with a minimum intake of 1.2 gm/kg/day. The nutritional recommendations for sarcopenia in 2010 made the following comment: “Many commentators have argued that the recommended daily allowance for protein, although sufficient for healthy individuals, fails to prevent muscle loss with aging. In addition, it is recommended that the amount of protein ingested should be spread equally throughout the day, i.e., equivalent amounts at breakfast, lunch, and dinner. If additional protein supplementation is given it should be administered between meals. Levels of protein intake as high as 1.6 g of protein/kg/d have been demonstrated to increase

exercise-induced muscle hypertrophy in older persons. Another study found that 1.0 g of protein/kg/d was the minimal amount required to maintain muscle mass. For these reasons it is recommended that older persons ingest between 1.0 and 1.5 g of protein/kg/d. The 2019 position statement from Bauer et al. support this approach: "A protein intake of 1 to 1.5 g/kg/day in conjunction with physical exercise seems reasonable for a person with sarcopenia" [79]. Finally, Pedersen and Cederholm note that based on prospective cohort studies suggest a safe intake of up to at least 1.2-1.5 g protein/kg [82]. Whereas these recommendations for nutritional management of sarcopenia were not limited to person with T2DM, they are likely applicable to this patient group.

Finally, he ADA, the European Society for Clinical Nutrition and Metabolism (ESPEN) as well as Mesinovic's review all caution about excessive weight loss strategies in overweight adults with diabetes. The use of nutritional supplements specifically targeted at persons with diabetes and sarcopenia has little or conflicting support.

In summary, patients with sarcopenia, including those with T2DM, generally have lower caloric/nutritional intake. General nutritional guidance recommends adequate caloric intake including specific recommendations for protein intake. Nutritional supplements are not uniformly recommended. Each of these recommendations is based on observational data rather than nutrition intervention data.

### *9.2 Lifestyle Interventions: Physical Activity*

Whereas physical activity is broadly recommended for the management of diabetes and exercise regimens in persons with sarcopenia show benefit [72], the data on specific types of activity to reduce the risk for sarcopenia in diabetes are more limited. Steffl's metanalysis of the relationship of physical activity in sarcopenia suggests that there is a potential reduction in the risk for sarcopenia of about 50%. This study has no specific information on diabetes patients. There are small, but informative, observational and intervention studies in T2DM. Gao et al. performed a metanalysis of 14 prospective studies (RCTs n = 11) with a total of 443 patients with diabetes and sarcopenia [74]. These studies used a variety of interventions and end point measures. However, among the various end points, two were clearly favorably affected by the exercise intervention: sit to stand and timed up and go. The latter was defined as defined as a test where subjects were asked to rise from a standard armchair, walk to a marker 3 m away, turn, walk back, and sit down again. Whereas this metanalysis did not demonstrate the effects of interventions on hand strength, leg strength or walking speed, the authors suggested that this might be the result of different study interventions, variable study durations and the comparatively small numbers of participants in each study. In the study by Kim (noted above), measures of physical activity including flexibility exercise, resistance training, moderate intensity physical activity and vigorous physical activity in men were all lowest with Sarcopenic Diabetes than the other 4 group, followed by diabetes alone and then sarcopenia alone. In women, the results were directionally similar, but for each category women with Sarcopenic diabetes (and the other categories) were generally less active than men. Of note in this study was the observation that HOMA IR, a measure of insulin resistance, was higher in both diabetes groups. In addition, in the Sarcopenic diabetes group triglycerides were higher and HDLc was lower than in all other groups. The TG to HDL ratio is considered a surrogate for insulin resistance. This observation supports other data that suggest that insulin resistance plays a role in the development of sarcopenia. Overall these data in Kim's study support the concept that increasing

both resistance training and aerobic exercise may be beneficial in sarcopenic diabetes perhaps mediated by improvements in insulin resistance as well as generally physical well-being. Park et al. used a later version of KNHANES (2014-2019) and studied community dwelling adults aged ≥65 (n = 7558) and analyzed aerobic exercise, resistance exercise and sedentary behavior on dynapenia [75]. They do make the distinction between dynapenia (age related decline in muscle strength) and sarcopenia (loss of both strength and muscle mass with aging). Dynapenia was described as a handgrip strength of <28 kg for men and <18 kg for women [17]. In a series of models adjusted for multiple lifestyle and co-morbidity variables both low aerobic exercise and low resistance exercise were associated with dynapenia. Low sedentary time was not associated with dynapenia in diabetes in contrast to other disease states such as cardiovascular disease and chronic lung disease. The observations of aerobic and resistance exercise in dynapenia are generally concordant with the results with sarcopenia in the Kim study [71]. As noted above, prospective intervention studies of activity in patients with diabetes and sarcopenia are limited. However, in general, these analyses support the benefits of exercise interventions in patients with diabetes and sarcopenia. The report by Boonpor et al. showing a relationship of grip strength and walking with CV outcomes is of interest in the context of the above observations [49]. Finally, Chien et al. performed a 12 week intervention study of resistance training in patients with diabetes and sarcopenia [73] using sand bags with progressively increasing weights in five exercises: arm curl, overhead press, hip adduction/abduction, step and tiptoe. There were 20 participants in both the training and control groups. At the end of the study, in addition to a favorable improvement in HbA1c, the active training group had improvements in upper extremity strength, muscle mass, and better sit-to-stand performance.

In summary, the data above support the benefits of physical activity in patients with diabetes and sarcopenia. The most interesting and compelling data are the effects of resistance training on not only muscle mass and function, but the suggestion that such training may also be associated with a reduction in insulin resistance, an important metabolic defect in T2DM.

## 10. Summary and Conclusions

Sarcopenia prevalence is increased in patients with DM. There are a number of potential mechanistic links, but causality is uncertain. The complications of DM including renal disease, neuropathy and cardiovascular disease are associated with even greater risks for sarcopenia. Approaches to mitigating sarcopenia in diabetes include glycemic control, especially with agents that may have anabolic effects, and exercise regimens, especially resistance exercises. Specific nutritional strategies in patients with DM and sarcopenia are sparse, including diet composition and potential adverse effects of weight loss in overweight/obese patients with DM. Nutrition composition recommended for diabetes management seem prudent in patients who also have sarcopenia. Conversely, nutrition recommendations for persons with sarcopenia are likely appropriate for persons with T2DM.

**Abbreviations**

| | |
|---|---|
| ADA | American Diabetes Association |
| AWGS | Asian Working Group for Sarcopenia |
| BMI | Body Mass Index |
| CVD | Cardiovascular Disease |
| DPN | Diabetic Peripheral Neuropathy |
| DPP4 inhibitor | Dipeptidyl Dipeptidase inhibitor |
| eGFR | estimated Glomerular Filtration Rate |
| EWGSOP | European Working Group of Sarcopenia in Older People |
| GLP1RA | Glucagon-Like Peptide 1 Receptor Agonists |
| HF | Heart Failure |
| KNHANES | Korean National Health and Nutrition Survey |
| MI | Myocardial Infarction |
| NHANES | National Health and Nutrition Survey |
| NIH | National Institutes of Health |
| RCT | Randomized Clinical Trial |
| SGLT2 inhibitor | Sodium-Glucose Co-Transporter 2 inhibitor |
| T2DM | Type 2 Diabetes Mellitus |
| TZD | Thiazolidinedione |

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**References**

1. Johri N, Vengat M, Kumar D, Nagar P, John D, Dutta S, et al. A comprehensive review on the risks assessment and treatment options for sarcopenia in people with diabetes. J Diabetes Metab Disord. 2023; 22: 995-1010.
2. Khan MA, Hashim MJ, King JK, Govender RD, Mustafa H, Al Kaabi J. Epidemiology of type 2 diabetes—Global burden of disease and forecasted trends. J Epidemiol Glob Health. 2020; 10: 107-111.
3. Cruz-Jentoft AJ, Landi F. Sarcopenia. Clin Med. 2014; 14: 183-186.

4. Marzetti E, Calvani R, Tosato M, Cesari M, Di Bari M, Cherubini A, et al. Sarcopenia: An overview. Aging Clin Exp Res. 2017; 29: 11-17.
5. Cacciatore S, Calvani R, Esposito I, Massaro C, Gava G, Picca A, et al. Emerging targets and treatments for sarcopenia: A narrative review. Nutrients. 2024; 16: 3271.
6. Petermann-Rocha F, Balntzi V, Gray SR, Lara J, Ho FK, Pell JP, et al. Global prevalence of sarcopenia and severe sarcopenia: A systematic review and meta-analysis. J Cachexia Sarcopenia Muscle. 2022; 13: 86-99.
7. Morley JE, Argiles JM, Evans WJ, Bhasin S, Cella D, Deutz NE, et al. Nutritional recommendations for the management of sarcopenia. J Am Med Dir Assoc. 2010; 11: 391-396.
8. Evans WJ, Guralnik J, Cawthon P, Appleby J, Landi F, Clarke L, et al. Sarcopenia: No consensus, no diagnostic criteria, and no approved indication-How did we get here? Geroscience. 2024; 46: 183-190.
9. American Diabetes Association Professional Practice Committee. 2. Diagnosis and classification of diabetes: Standards of care in diabetes-2024. Diabetes Care. 2024; 47: S20-S42.
10. Hoogwerf BJ. Type of diabetes mellitus: Does it matter to the clinician? Cleve Clin J Med. 2020; 87: 100-108.
11. Pleus S, Tytko A, Landgraf R, Heinemann L, Werner C, Muller-Wieland D, et al. Definition, classification, diagnosis and differential diagnosis of diabetes mellitus: Update 2023. Exp Clin Endocrinol Diabetes. 2024; 132: 112-124.
12. Defronzo RA. Banting lecture. From the triumvirate to the ominous octet: A new paradigm for the treatment of type 2 diabetes mellitus. Diabetes. 2009; 58: 773-795.
13. Salom Vendrell C, Garcia Tercero E, Moro Hernandez JB, Cedeno-Veloz BA. Sarcopenia as a little-recognized comorbidity of type II diabetes mellitus: A review of the diagnosis and treatment. Nutrients. 2023; 15: 4149.
14. Shafiee G, Keshtkar A, Soltani A, Ahadi Z, Larijani B, Heshmat R. Prevalence of sarcopenia in the world: A systematic review and meta- analysis of general population studies. J Diabetes Metab Disord. 2017; 16: 21.
15. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, et al. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on sarcopenia in older people. Age Ageing. 2010; 39: 412-423.
16. Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyere O, Cederholm T, et al. Sarcopenia: Revised European consensus on definition and diagnosis. Age Ageing. 2019; 48: 601.
17. Chen LK, Woo J, Assantachai P, Auyeung TW, Chou MY, Iijima K, et al. Asian working group for sarcopenia: 2019 consensus update on sarcopenia diagnosis and treatment. J Am Med Dir Assoc. 2020; 21: 300-307.e2.
18. Chen LK, Liu LK, Woo J, Assantachai P, Auyeung TW, Bahyah KS, et al. Sarcopenia in Asia: Consensus report of the Asian Working Group for sarcopenia. J Am Med Dir Assoc. 2014; 15: 95-101.
19. Fielding RA, Vellas B, Evans WJ, Bhasin S, Morley JE, Newman AB, et al. Sarcopenia: An undiagnosed condition in older adults. Current consensus definition: Prevalence, etiology, and consequences. International working group on sarcopenia. J Am Med Dir Assoc. 2011; 12: 249-256.

20. Studenski SA, Peters KW, Alley DE, Cawthon PM, McLean RR, Harris TB, et al. The FNIH sarcopenia project: Rationale, study description, conference recommendations, and final estimates. J Gerontol A Biol Sci Med Sci. 2014; 69: 547-558.
21. Voulgaridou G, Tyrovolas S, Detopoulou P, Tsoumana D, Drakaki M, Apostolou T, et al. Diagnostic criteria and measurement techniques of sarcopenia: A critical evaluation of the up-to-date evidence. Nutrients. 2024; 16: 436.
22. Bhasin S, Travison TG, Manini TM, Patel S, Pencina KM, Fielding RA, et al. Sarcopenia definition: The position statements of the sarcopenia definition and outcomes consortium. J Am Geriatr Soc. 2020; 68: 1410-1418.
23. Chanda D, Ha H, Lee IK. Editorial: The role of oxidative stress and systemic inflammation in diabetes and chronic kidney disease. Front Endocrinol. 2023; 14: 1272525.
24. Oda Y, Nishi H, Nangaku M. Role of inflammation in progression of chronic kidney disease in type 2 diabetes mellitus: Clinical implications. Semin Nephrol. 2023; 43: 151431.
25. Yousef H, Khandoker AH, Feng SF, Helf C, Jelinek HF. Inflammation, oxidative stress and mitochondrial dysfunction in the progression of type II diabetes mellitus with coexisting hypertension. Front Endocrinol. 2023; 14: 1173402.
26. Zhao L, Hu H, Zhang L, Liu Z, Huang Y, Liu Q, et al. Inflammation in diabetes complications: Molecular mechanisms and therapeutic interventions. MedComm. 2024; 5: e516.
27. Kim J, Lee JY, Kim CY. A Comprehensive review of pathological mechanisms and natural dietary ingredients for the management and prevention of sarcopenia. Nutrients. 2023; 15: 2625.
28. Purnamasari D, Tetrasiwi EN, Kartiko GJ, Astrella C, Husam K, Laksmi PW. Sarcopenia and chronic complications of type 2 diabetes mellitus. Rev Diabet Stud. 2022; 18: 157-165.
29. Witham MD, Granic A, Pearson E, Robinson SM, Sayer AA. Repurposing drugs for diabetes mellitus as potential pharmacological treatments for sarcopenia—A narrative review. Drugs Aging. 2023; 40: 703-719.
30. Landi F, Onder G, Bernabei R. Sarcopenia and diabetes: Two sides of the same coin. J Am Med Dir Assoc. 2013; 14: 540-541.
31. Lisco G, Disoteo OE, De Tullio A, De Geronimo V, Giagulli VA, Monzani F, et al. Sarcopenia and diabetes: A detrimental liaison of advancing age. Nutrients. 2023; 16: 63.
32. Tack W, De Cock AM, Dirinck EL, Bastijns S, Arien F, Perkisas S. Pathophysiological interactions between sarcopenia and type 2 diabetes: A two-way street influencing diagnosis and therapeutic options. Diabetes Obes Metab. 2024; 26: 407-416.
33. Anagnostis P, Gkekas NK, Achilla C, Pananastasiou G, Taouxidou P, Mitsiou M, et al. Type 2 diabetes mellitus is associated with increased risk of sarcopenia: A systematic review and meta-analysis. Calcif Tissue Int. 2020; 107: 453-463.
34. Veronese N, Pizzol D, Demurtas J, Soysal P, Smith L, Sieber C, et al. Association between sarcopenia and diabetes: A systematic review and meta-analysis of observational studies. Eur Geriatr Med. 2019; 10: 685-696.
35. Izzo A, Massimino E, Riccardi G, Della Pepa G. A Narrative review on sarcopenia in type 2 diabetes mellitus: Prevalence and associated factors. Nutrients. 2021; 13: 183.
36. Ai Y, Xu R, Liu L. The prevalence and risk factors of sarcopenia in patients with type 2 diabetes mellitus: A systematic review and meta-analysis. Diabetol Metab Syndr. 2021; 13: 93.
37. Dai S, Shu D, Meng F, Chen Y, Wang J, Liu X, et al. Higher risk of sarcopenia in older adults with type 2 diabetes: NHANES 1999-2018. Obes Facts. 2023; 16: 237-248.

38. Chung HS, Hwang SY, Choi JH, Lee HJ, Yoo HJ, Seo JA, et al. Effects of low muscle mass on albuminuria and chronic kidney disease in patients with type 2 diabetes: The Korean Sarcopenic Obesity Study (KSOS). J Gerontol A Biol Sci Med Sci. 2018; 73: 386-392.
39. Formiga F, Moreno-Gonzalez R, Corsonello A, Carlsson A, Arnlov J, Mattace-Raso F, et al. Diabetes, sarcopenia and chronic kidney disease; the Screening for CKD among older people across Europe (SCOPE) study. BMC Geriatr. 2022; 22: 254.
40. Lee C, Kim HJ, Chang TI, Kang EW, Joo YS, Kim HW, et al. Synergic association of diabetes mellitus and chronic kidney disease with muscle loss and cachexia: Results of a 16-year longitudinal follow-up of a community-based prospective cohort study. Aging. 2021; 13: 21941-21961.
41. Low S, Pek S, Moh A, Khin CY, Lim CL, Ang SF, et al. Low muscle mass is associated with progression of chronic kidney disease and albuminuria—An 8-year longitudinal study in Asians with type 2 diabetes. Diabetes Res Clin Pract. 2021; 174: 108777.
42. Oosterwijk MM, Navis G, Bakker SJ, Laverman GD. Personalized nutrition in patients with type 2 diabetes and chronic kidney disease: The two-edged sword of dietary protein intake. J Pers Med. 2022; 12: 300.
43. Seo DH, Suh YJ, Cho Y, Ahn SH, Seo S, Hong S, et al. Effect of low skeletal muscle mass and sarcopenic obesity on chronic kidney disease in patients with type 2 diabetes. Obesity. 2022; 30: 2034-2043.
44. Zanetti M, Barazzoni R, Kiwanuka E, Vettore M, Vedovato M, Tessari P. Accelerated whole-body protein catabolism in subjects with type 2 diabetes mellitus and albuminuria. PLoS One. 2020; 15: e0243638.
45. Han E, Lee YH, Kim G, Kim SR, Lee BW, Kang ES, et al. Sarcopenia is associated with albuminuria independently of hypertension and diabetes: KNHANES 2008-2011. Metabolism. 2016; 65: 1531-1540.
46. Ida S, Kaneko R, Imataka K, Murata K. Association between sarcopenia and renal function in patients with diabetes: A systematic review and meta-analysis. J Diabetes Res. 2019; 2019: 1365189.
47. Bouchi R, Fukuda T, Takeuchi T, Minami I, Yoshimoto T, Ogawa Y. Sarcopenia is associated with incident albuminuria in patients with type 2 diabetes: A retrospective observational study. J Diabetes Investig. 2017; 8: 783-787.
48. Yang R, Zhang Y, Shen X, Yan S. Sarcopenia associated with renal function in the patients with type 2 diabetes. Diabetes Res Clin Pract. 2016; 118: 121-129.
49. Boonpor J, Pell JP, Ho FK, Celis-Morales C, Gray SR. In people with type 2 diabetes, sarcopenia is associated with the incidence of cardiovascular disease: A prospective cohort study from the UK biobank. Diabetes Obes Metab. 2024; 26: 524-531.
50. Song E, Hwang SY, Park MJ, Jang A, Kim KJ, Yu JH, et al. Additive impact of diabetes and sarcopenia on all-cause and cardiovascular mortality: A longitudinal nationwide population-based study. Metabolism. 2023; 148: 155678.
51. Massimino E, Izzo A, Castaldo C, Ferretti E, Rivellese AA, Della Pepa G. Risk of sarcopenia and associated factors in older adults with type 2 diabetes: An exploratory cross-sectional study. Healthcare. 2023; 11: 2081.
52. Mikura K, Kodama E, Iida T, Imai H, Hashizume M, Kigawa Y, et al. Association between sarcopenia and the severity of diabetic polyneuropathy assessed by nerve conduction studies in Japanese patients with type 2 diabetes mellitus. J Diabetes Investig. 2022; 13: 1357-1365.

53. Mohapatra S, Ramachandran M, Behera KK, Priyadarsini N, Nanda P, Devi S. Association of peripheral neuropathy with skeletal muscle mass and function in type two diabetes mellitus patients: A cross-sectional study. Endocrinol Diabetes Nutr. 2022; 69: 591-599.
54. Oh TJ, Song Y, Moon JH, Choi SH, Jang HC. Diabetic peripheral neuropathy as a risk factor for sarcopenia. Ann Geriatr Med Res. 2019; 23: 170-175.
55. Sarodnik C, Bours SPG, Schaper NC, van den Bergh JP, van Geel T. The risks of sarcopenia, falls and fractures in patients with type 2 diabetes mellitus. Maturitas. 2018; 109: 70-77.
56. Sravya SL, Swain J, Sahoo AK, Mangaraj S, Kanwar J, Jadhao P, et al. Sarcopenia in type 2 diabetes mellitus: Study of the modifiable risk factors involved. J Clin Med. 2023; 12: 5499.
57. Wannarong T, Sukpornchairak P, Naweera W, Geiger CD, Ungprasert P. Association between diabetic peripheral neuropathy and sarcopenia: A systematic review and meta-analysis. Geriatr Gerontol Int. 2022; 22: 785-789.
58. Xu H, Xiang QY, Zhan JK, Wang Y, Wang YJ, Li S, et al. Association between macro- and microvascular damage and sarcopenia index in individuals with type 2 diabetes mellitus. Appl Physiol Nutr Metab. 2024; 49: 762-772.
59. Yasemin O, Seydahmet A, Ozcan K. Relationship between diabetic neuropathy and sarcopenia. Prim Care Diabetes. 2019; 13: 521-528.
60. American Diabetes Association Professional Practice Committee. 10. Cardiovascular disease and risk management: Standards of care in diabetes-2024. Diabetes Care. 2024; 47: S179-S218.
61. Zhang Y, Shen X, He L, Zhao F, Yan S. Association of sarcopenia and muscle mass with both peripheral neuropathy and nerve function in patients with type 2 diabetes. Diabetes Res Clin Pract. 2020; 162: 108096.
62. Cheng Z, Li X, Xu H, Bao D, Mu C, Xing Q. Incidence of accidental falls and development of a fall risk prediction model among elderly patients with diabetes mellitus: A prospective cohort study. J Clin Nurs. 2023; 32: 1398-1409.
63. Hicks CW, Wang D, Daya N, Juraschek SP, Matsushita K, Windham BG, et al. The association of peripheral neuropathy detected by monofilament testing with risk of falls and fractures in older adults. J Am Geriatr Soc. 2023; 71: 1902-1909.
64. Timar B, Timar R, Gaita L, Oancea C, Levai C, Lungeanu D. The impact of diabetic neuropathy on balance and on the risk of falls in patients with type 2 diabetes mellitus: A cross-sectional study. PLoS One. 2016; 11: e0154654.
65. Cederholm T, Cruz-Jentoft AJ, Maggi S. Sarcopenia and fragility fractures. Eur J Phys Rehabil Med. 2013; 49: 111-117.
66. Alfaro-Alvarado FA, Rosas-Barrientos JV, Ocharan-Hernandez ME, Diaz-Chiguer D, Vargas-De-Leon C. Association between sarcopenia and poor glycemic control in older adults with type 2 diabetes mellitus. Diseases. 2023; 11: 175.
67. Ma XY, Chen FQ. Effects of anti-diabetic drugs on sarcopenia: Best treatment options for elderly patients with type 2 diabetes mellitus and sarcopenia. World J Clin Cases. 2021; 9: 10064-10074.
68. Massimino E, Izzo A, Riccardi G, Della Pepa G. The impact of glucose-lowering drugs on sarcopenia in type 2 diabetes: Current evidence and underlying mechanisms. Cells. 2021; 10: 1958.
69. Pan R, Zhang Y, Wang R, Xu Y, Ji H, Zhao Y. Effect of SGLT-2 inhibitors on body composition in patients with type 2 diabetes mellitus: A meta-analysis of randomized controlled trials. PLoS One. 2022; 17: e0279889.

70. Zhang S, Qi Z, Wang Y, Song D, Zhu D. Effect of sodium-glucose transporter 2 inhibitors on sarcopenia in patients with type 2 diabetes mellitus: A systematic review and meta-analysis. Front Endocrinol. 2023; 14: 1203666.
71. Kim M, Kobori T. Association of a combination of sarcopenia and type 2 diabetes with blood parameters, nutrient intake, and physical activity: A nationwide population-based study. Nutrients. 2023; 15: 4955.
72. Shen Y, Shi Q, Nong K, Li S, Yue J, Huang J, et al. Exercise for sarcopenia in older people: A systematic review and network meta-analysis. J Cachexia Sarcopenia Muscle. 2023; 14: 1199-1211.
73. Chien YH, Tsai CJ, Wang DC, Chuang PH, Lin HT. Effects of 12-week progressive sandbag exercise training on glycemic control and muscle strength in patients with type 2 diabetes mellitus combined with possible sarcopenia. Int J Environ Res Public Health. 2022; 19: 15009.
74. Gao S, Yu L, Yi G, Li T, Chen Z, Ding J. Exercise intervention as a therapy in patients with diabetes mellitus and sarcopenia: A meta-analysis. Diabetes Ther. 2022; 13: 1311-1325.
75. Park JH, Nam HS, Park M, Kim YH. Differential association between physical activity behaviours and dynapenia by comorbid diseases in community-dwelling Korean older adults. Eur Rev Aging Phys Act. 2024; 21: 6.
76. Locatelli JC, Costa JG, Haynes A, Naylor LH, Fegan PG, Yeap BB, et al. Incretin-based weight loss pharmacotherapy: Can resistance exercise optimize changes in body composition? Diabetes Care. 2024; 47: 1718-1730.
77. Osaka T, Hamaguchi M, Fukui M. Favorable appendicular skeletal muscle mass changes in older patients with type 2 diabetes receiving GLP-1 receptor agonist and basal insulin co-therapy. Clin Med Insights Endocrinol Diabetes. 2023; 16. doi: 10.1177/11795514231161885.
78. American Diabetes Association Professional Practice Committee. 9. Pharmacologic approaches to glycemic treatment: Standards of care in diabetes-2024. Diabetes Care. 2024; 47: S158-S178.
79. Bauer J, Morley JE, Schols A, Ferrucci L, Cruz-Jentoft AJ, Dent E, et al. Sarcopenia: A time for action. An SCWD position paper. J Cachexia Sarcopenia Muscle. 2019; 10: 956-961.
80. Bosaeus I, Rothenberg E. Nutrition and physical activity for the prevention and treatment of age-related sarcopenia. Proc Nutr Soc. 2016; 75: 174-180.
81. Won CW. Management of sarcopenia in primary care settings. Korean J Fam Med. 2023; 44: 71-75.
82. Pedersen AN, Cederholm T. Health effects of protein intake in healthy elderly populations: A systematic literature review. Food Nutr Res. 2014; 58: 23364.