DSX 17 (2023) 102835

Contents lists available at ScienceDirect

Diabetes & Metabolic Syndrome: Clinical Research & Reviews

journal homepage: www.elsevier.com/locate/dsx

Sarcopenia and type 2 diabetes: Pathophysiology and potential therapeutic lifestyle interventions

Alexis Marcotte-Chénard [a], Barbara Oliveira [b], Jonathan P. Little [b], Darren G. Candow [c,*]

[a] Faculty of Physical Activity Sciences, University of Sherbrooke, Sherbrooke, QC, J1K 2R1, Canada
[b] School of Health and Exercise Sciences, The University of British Columbia, Okanagan Campus, Kelowna, BC, V1V 1V7, Canada
[c] Faculty of Kinesiology & Health Studies, University of Regina, Saskatchewan, S4S 0A2, Canada

ARTICLE INFO

Keywords:
T2D
Sarcopenia
Exercise
Nutrition
Diet

ABSTRACT

Aims: Sarcopenia generally refers to the age-related reduction in muscle strength, functional ability, and muscle mass. Sarcopenia is a multifactorial condition associated with poor glucose disposal, insulin resistance, and subsequently type 2 diabetes (T2D). The pathophysiological connection between sarcopenia and T2D is complex but likely involves glycemic control, inflammation, oxidative stress, and adiposity. **Methods and Results:** Resistance exercise and aerobic training are two lifestyle interventions that may improve glycemic control in older adults with T2D and counteract sarcopenia. Further, there is evidence that dietary protein, Omega-3 fatty acids, creatine monohydrate, and Vitamin D hold potential to augment some of these benefits from exercise. **Conclusions:** The purpose of this narrative review is: (1) discuss the pathophysiological link between age-related sarcopenia and T2D, and (2) discuss lifestyle interventions involving physical activity and nutrition that may counteract sarcopenia and T2D.

1. Introduction

Sarcopenia generally refers to the age-related reduction in muscle performance (i.e., measures of muscle strength), functional ability [1], and muscle mass. As a point of clarification, lean tissue is routinely included in the diagnosis of sarcopenia in older adults as a substitute for muscle mass. However, lean tissue is a proxy surrogate and a poor indicator of muscle mass [2–4] as this proxy takes into account water and fibrotic tissue [2]. These non-contractile components can account for ~15% of total muscle area [5] leading to significant error and misdiagnosis of sarcopenia [1]. Furthermore, lean mass does not predict muscle strength [3,6] or pertinent health outcomes (e.g. mobility issues, hospital admission, activities of daily living) in older adults [1,2]. Therefore, for the purpose of this narrative review, sarcopenia will be defined as the age-related reduction in muscle strength, muscle mass, and functional ability.

During lifespan, the median annual rate of muscle loss is 0.47% in males and 0.37% in females and it drastically accelerates after 75 years of age (−0.80 to −0.98% in males and −0.64 to −0.70% in females [7]). The rate of muscle strength loss is even more important, with a study reporting strength reduction between 2 and 4% annually (knee extensor strength measured by isokinetic dynamometry [8]). From a global health perspective, treating sarcopenia has become such an important issue that the World Health Organization (WHO) recently established a code (International Classification of Diseases and Related Health Problems [ICD-10-CM] [M62.84]) for better diagnosis, assessment, and treatment of the age-related condition [9,10]. In recent years, several definitions of sarcopenia have emerged from various consensus groups (e.g., EWGSOP2, AWGS, SDOC [11]), with different definitions and diagnoses, making the management of the disease all the more difficult. In addition to the decrease in strength and functional capacity, sarcopenia is also associated with poor glucose disposal, insulin resistance, and decreased metabolic rate [12] which likely contributes to many sarcopenic older adults having type 2 diabetes (T2D) [13]. In 2017, almost a half billion people had T2D and based on population projections [12], the incidence of older adults living with both sarcopenia and T2D will likely increase.

A previous study by Mesinovic et al. [13] has underlined numerous potential mechanisms linking T2D and sarcopenia (e.g., insulin resistance, adiposity, oxidative stress) showing its bi-directional relationship. Nevertheless, it is important to note that these factors are not uniformly influential and may exert a distinct influence on one another.

* Corresponding author. Aging Muscle & Bone Health Laboratory Faculty of Kinesiology & Health Studies, 3737, Wascana Parkway, University of Regina, Regina, SK, S4S 0A2, Canada
E-mail address: darren.candow@uregina.ca (D.G. Candow).

https://doi.org/10.1016/j.dsx.2023.102835
Received 9 April 2023; Received in revised form 25 July 2023; Accepted 29 July 2023
Available online 1 August 2023

Certain factors are prone to heighten the risk of type 2 diabetes, consequently leading to the onset of sarcopenia, whereas other factors are more likely to escalate the risk of sarcopenia, resulting in the development of T2D. The sequential onset of these pathologies is an important aspect to consider, as therapeutic interventions, such as exercise and nutrition, will be modulated accordingly. Therefore, the development of specific non-pharmaceutical guidelines for the prevention and treatment of both diseases is essential to optimize patient health and ultimately decrease the risk of premature mortality within that population [14,15]. Therefore, the purpose of this narrative review is: (1) discuss the pathophysiological link between age-related sarcopenia and T2D and how each condition influences the development of the other and (2) discuss lifestyle interventions involving physical activity and nutrition that may counteract sarcopenia and T2D and provide specific recommendations for healthcare providers.

2. Sarcopenia pathophysiology

Sarcopenia is a multifactorial phenomenon involving numerous intertwined complex processes encompassing changes associated with the central and peripheral nervous system, neuromuscular junction, vasculature, subsarcolemmal milieu, inflammatory and endocrine response to cellular stressors, and gut microbiome (for detailed reviews see Refs. [16–23]). Fig. 1 provides a summary of the numerous pathways that may be directly or indirectly responsible for the development and exacerbation of sarcopenia.

3. Sarcopenia and type 2 diabetes: interconnected clinical conditions

Individuals with T2D have a 2–3x higher prevalence of having sarcopenia [24] and sarcopenia has recently been recognized as a complication in T2D with a prevalence ranging from 7% to 29.3% [25]. T2D is a metabolic disorder characterized by hyperglycemia and altered lipid metabolism that results from reduced insulin action in tissues and inappropriate insulin secretion from pancreatic beta cells [26]. Insulin resistance in skeletal muscle is typically caused by the desensitization to insulin released by the pancreas, resulting in impaired glucose disposal, inevitably contributing to elevated blood glucose concentrations (upon which the diagnostic criteria for T2D are based) [27]. An increase in adiposity and a decrease in skeletal muscle mass (largest tissue for glucose disposal) and function (i.e., sarcopenic obesity) are major contributing factors in the development of insulin resistance [28,29]. Sarcopenic obesity is aggravated by the biological process of aging and is associated with increases in the incidence and prevalence of T2D [30]. A progressive and generalized loss of muscle quantity, quality (mass relative to force-generating capacity), and function is typically observed starting in the 4th decade and progresses over time inevitably contributing to sarcopenia [25]. Bidirectionally, the risk of sarcopenia is increased in people with T2D and older adults with sarcopenia may have an increased risk of developing T2D [13]. Each disorder exacerbates the consequences of the other resulting in functional decline and disability [13,29].

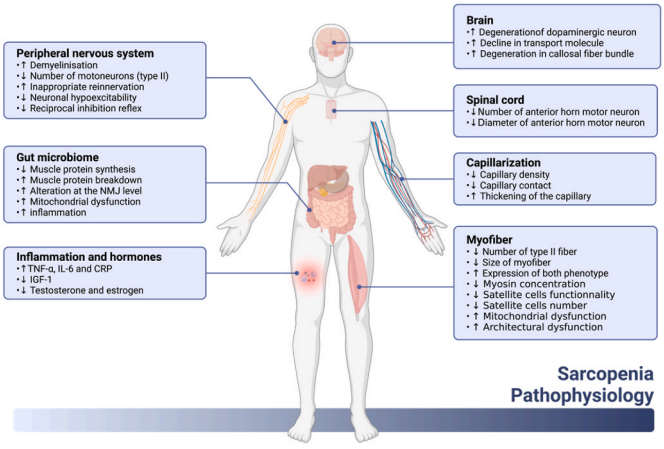

Fig. 1. Factors influencing the development of sarcopenia.
This figure presents a comprehensive depiction of the variables that exert influence over the development and progression of sarcopenia. It is noteworthy that a significant portion of these components do not operate in isolation but rather engage in intricate interactions with one another. NMJ = neuromuscular junction; TNF-a = Tumor necrosis factor-alpha; CRP=C reactive protein; Insulin-like growth factor 1; Figure inspired by Falkenhain and colleagues [142].

3.1. Potential mechanisms by which sarcopenia may lead to T2D

Sarcopenia may contribute to the development and progression of T2D by altering glucose disposal due to the loss of muscle mass, increased inflammation and oxidative stress, and muscular adipose tissue accumulation [31].

3.1.1. Muscle mass and glycemic control

Lower muscle mass could result in reduced glycemic control since skeletal muscle is estimated to be responsible for ~80% of glucose disposal in response to infused glucose [32]. A prospective observational cohort study with 1160 participants showed that a reduction of muscle mass over a five-year time span was a risk factor for T2D susceptibility [33]. The skeletal muscle loss might lead to diminished insulin-mediated glucose disposal and exacerbated insulin resistance independent of obesity in sarcopenia, resulting in hyperglycemia [34]. Similarly, Sugimoto and colleagues have demonstrated that among patients with T2D and sarcopenia, poor glycemic control (assessed by HbA1c) was associated with low skeletal mass index [35]. It is important to note that there is disagreement concerning the interaction between fat-free mass (FFM) (proxy measure of muscle mass), and metabolic health, with studies reporting no protective effect of FFM on T2D incidence [36] or even a deleterious effect of higher appendicular lean mass [37]. These discrepancies could partially be explained by the way FFM is reported. Indeed, in our recent article we showed that the prevalence of the metabolic syndrome decreases with increasing quartile of whole-body fat-free mass (FFM) presented as percentage (from 40% in Q1 *vs.* 10% in Q4), while the opposite trend was observed when FFM was presented relative to height (FFM/Height^2; Q1: 10% to Q4: 44% [38]). It is therefore important that researchers and knowledge users exercise caution when assessing the beneficial effect of muscle mass on metabolic health knowing that the way it is measured (e.g. DXA *vs.* D3-creatine *vs.* MRI [11]), and represented [absolute FFM *vs.* relative to squared height (FFMi) *vs.* relative to body weight (%)] could directly influence this relationship [38].

3.1.2. Oxidative stress, inflammation and insulin

Dysfunctional skeletal muscle (e.g., atrophy, accumulation of fat, decreased mitochondrial content) presents reduced antioxidative capacity and can lead to increased production of reactive oxygen species and overactivation of pro-inflammatory processes. As mentioned above, oxidative stress impairs insulin signaling and disturbs glucose uptake in skeletal muscle, and could contribute to hyperglycemia [34]. For example, advanced glycation end products (AGEs) concentrations increase with aging and are associated with insulin resistance [39]. Other mechanisms proposed to imply that sarcopenia could be a causal factor for insulin resistance and development of T2D are through myokines counterbalancing the effect of adipokines on the insulin resistant state and the loss of type II muscle fibers (relevant to insulin resistance) rather than type I muscle fibers [40]. Additionally, fasting insulin is lower in people with sarcopenia, suggesting that reduction of endogenous secretion of insulin may be associated with sarcopenia and consequently

impaired MPS, all reinforced with aging [41].

3.1.3. Adiposity

Aging is typically associated with decreased basal metabolic rate and postprandial energy expenditure resulting in lower fat oxidation. The latter, coupled with sarcopenic obesity, is associated with an increased incidence of insulin resistance in older adults [42]. Muscle mass loss and aging skeletal muscle infiltrated by ectopic fat and intermuscular adipose tissue (IMAT) contribute to insulin resistance [34]. It appears that insulin resistance and loss of muscle mass independently or additively alter glucose homeostasis with aging [27].

In addition, due to IMAT's proximity to skeletal muscle, it could directly interfere with muscle insulin resistance, sensitivity and metabolic dysfunction [43]. It is proposed that IMAT secretes proteins that modify muscle's extracellular matrix, which is known to influence insulin sensitivity in adipose tissue, liver, and skeletal muscle [43]. Indeed Sachs et al. and Goodpaster et al. showed that IMAT triglyceride lipolysis increases free fatty acid concentration (*in vitro* and on the thigh, respectively), leading to muscle lipid accumulation and consequently insulin resistance [43,44].

In addition to insulin resistance, IMAT-caused inflammation is another possible mechanism underlying the pathogenesis of diabetes. Inflammatory markers, such as interleukin-6 and C-reactive protein are elevated when IMAT levels are higher [45]. For example, Kahn et al. showed that IMAT had higher secretion of inflammatory cytokines (IL2, IL18, IL27, FGF23, and CSF1) but also higher anti-inflammatory cytokines (IL10 and IL13) *in vitro* when compared to other adipose tissue depots. The same pattern was verified for inflammatory chemokines and some adipokines [46]. The increased infiltration of proinflammatory molecules leads to local muscle inflammation which may alter myocyte insulin sensitivity [46]. These data suggest that IMAT might be a negative contributor to skeletal muscle metabolism increasing metabolic risk and decreasing insulin sensitivity. In conclusion, impaired muscle health can contribute to the development and progression of T2D.

3.2. Potential mechanisms by which T2D may lead to sarcopenia

3.2.1. Insulin resistance and skeletal muscle

Skeletal muscle is the major insulin-stimulated glucose disposal tissue making it an important mediator of glucose homeostasis [47]. The actions of insulin in skeletal muscle may be progressively reduced in those with T2D due to low insulin sensitivity and beta-cell dysfunction [25]. Insulin resistance impairs glucose uptake and disposal into skeletal muscle, which could contribute to reduced muscle mass and force-generating capacity [48]. Adults with T2D experience mild muscle atrophy in middle age which intensifies with advancing age [49]. Atrophy of skeletal muscle fibers and qualitative changes in muscle tissue could lead to a decline in muscle strength and sarcopenia. Therefore, people with T2D tend to have lower muscular strength and are more likely to have decreased functional ability compared to healthy individuals [50].

3.2.2. Intermuscular adipose tissue and inflammation

IMAT levels are influenced by factors such as age, chronic disease, obesity and inactivity [51]. Therefore, people living with T2D with increased IMAT are more vulnerable to impaired muscle function and progression of sarcopenia [52]. It is believe that higher content of IMAT may increase muscle fibrosis, and could influence the development of sarcopenia, age-related metabolic dysfunction, as well as the greater declines in these parameters in individuals with T2D [53]. This generates a cycle of increased IMAT, insulin resistance, inflammation, and mobility and muscle dysfunctions [51]. In fact, fat accumulation in skeletal muscle promotes reactive oxygen species (ROS) formation, and inflammation through increased local pro-inflammatory cytokines and free fatty acids leading to insulin resistance [54]. On the other hand, T2D is associated with chronic, low-grade systemic inflammation and higher levels of interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and C-reactive protein (CRP) [55]. Chronic low-grade inflammation is also a primary contributing factor and consequence of sarcopenia, referred to as 'inflammaging' [56]. Therefore, it appears that IMAT may be both a target and a source of inflammation acting as cause and consequence of muscle dysfunction and type 2 diabetes.

3.2.3. Oxidative stress

Mechanistic links between sarcopenia, T2D and oxidative stress are evident. Aging leads to reduced antioxidant capacity [57] and T2D results in higher generation of reactive oxygen species [58] through altered lipid metabolism, insulin resistance, increased AGEs, and mitochondrial dysfunction. Olson et al. [57] described the role that AGEs play in peripheral nerve neuropathy, but it is still unclear whether AGEs promote denervation in aging skeletal muscle and/or contribute to sarcopenic muscle. Moreover, abnormal mitochondrial form and function could influence glucose disposal rate and insulin sensitivity but research remains inconclusive [59]. Chronic hyperglycemia, generation of AGEs in skeletal muscle, as well as the presence of comorbidities (especially neuropathy), may hinder muscle energetics and contribute to the development of sarcopenia [25,29].

3.2.4. Microvascular and macrovascular complications

Microvascular complications refer to damage to the small blood vessels in the body, including the capillaries that supply oxygen and nutrients to the tissues. Decrease capillarization of the nervous system has been observed during aging altering the arterial physiology of the spinal cord in Wistar rats [60]. It is therefore possible that the change in capillarization observed in the spinal cords contributed to the loss of motoneurons, which is the main driver of muscle loss and strength with aging. Peripheral neuropathy is one of the most prevalent complications of diabetes ($\geq$20% [61]) and can considerably have a negative effect on one's quality of life [62]. In older individuals (50–87 years) with T2D, the presence of peripheral neuropathy reduces lower body force production (i.e., maximum isometric knee extension) [63]. Furthermore, poor peripheral nerve function is associated with attenuated lower body strength and functional ability (i.e., reduced balance, slow gait speed) [64]. Retinopathy and nephropathy, two other common complications observed in individuals with T2D, could also influence the development of sarcopenia (Reviewed in Ref. [13]). Briefly, retinopathy has been associated with sarcopenia and low muscle strength in individuals with T2D [65], while nephropathy is associated with persistent muscle protein catabolism, which leads to muscle atrophy [66]. The capillarization of the muscle is also of great importance knowing that an adequate capillary bed is required for oxygen, nutrients, and hormones delivery as well as heat and metabolites removal. Groen et al. [67] have shown a reduced capillary density (number of capillaries per mm^2), as well as capillary contact in older individuals with T2D compared to younger and older individuals. This reduced capillary density could create a non-favorable environment for the myofiber, subsequently affecting the anabolism and catabolism balance.

Among macrovascular complications, peripheral arterial disease (PAD) which is defined by the narrowing or blockage of the peripheral arteries by atherosclerosis, is two to seven-fold more prevalent in individuals living with T2D compared to those without the condition [68]. A study involving 135 older adults showed that people living with PAD have decreased muscle strength and gait speed [69]. Most individuals living with PAD have reduced calf skeletal muscle mass, increase IMAT, decrease peroneal nerve function, and reduce functional performance [70]. Intermittent claudication, one of the hallmark symptoms of PAD, could reduce physical activity levels [71], which ultimately could lead to a worsened health profile. Together, both micro- and macrovascular diseases associated with the non-adequate management of T2D may accelerate the onset and progression of sarcopenia.

3.2.5. Glycemic control

Ogama and colleagues showed that glucose fluctuations were independently associated with sarcopenia and among the components of sarcopenia, glucose fluctuations were significantly associated with low muscle mass, low grip strength, and slow walking speed [72]. Therefore, improving glucose control may be expected to beneficially impact some of the mechanisms involved in sarcopenia; in fact, many glucose-lowering medications can improve insulin sensitivity, inhibit AGEs formation, and improve inflammation and oxidative stress [73]. Along these lines, metformin, a first-line oral hypoglycemic drug, appears to play an important role in reducing the risk of sarcopenia. Chen et al. [74] demonstrated that participants who took metformin alone or combined with other drugs exhibited a lower risk for sarcopenia than those who took no medication. Rizzo and colleagues [75] showed that the DPP4-I therapy leads to better glycemic and inflammatory control, and it is also associated with better sarcopenic parameters, preservation of lean body mass, and strength and physical performance indices. Glucose-lowering therapy may improve muscle health by reducing blood glucose concentrations, which, as described above, can have negative effects on muscle through inflammation, oxidative stress, and increased AGEs if chronically elevated [13]. Fig. 2 provides a summary of the potential mechanisms influencing the development and progression of both sarcopenia and T2D. In light of these interconnected mechanisms of sarcopenia and T2D, exercise and nutritional interventions could be of benefit to the aging population to ameliorate both conditions.

4. Exercise and nutrition: potential therapeutic interventions

4.1. Resistance exercise

Resistance exercise is the primary non-pharmacological intervention for the treatment of sarcopenia [76]. A systematic review of eight randomized controlled trials (n > 500) using various definitions of sarcopenia found large effect sizes from resistance exercise on strength (hand-grip: standardized mean difference [SMD] = 0.81, 95% CI: 0.35, 1.27) and functional ability (habitual gait speed; SMD = 1.28, 95% CI: 0.36, 2.19; [77]. Lower-body strength (knee extension) is inversely associated with the ability to perform activities of daily living (i.e., walking, stair climbing, rising from a chair; [78,79]. A meta-analysis involving 43 RCT's (n > 600; mean age ~67yrs) showed that resistance exercise improved leg extension strength by 12.08 kg (95% CI: 10.44, 12.72 kg; p < 0.001; [80]. Further, it is well established that resistance exercise increases various measures of muscle accretion in older adults [81,82].

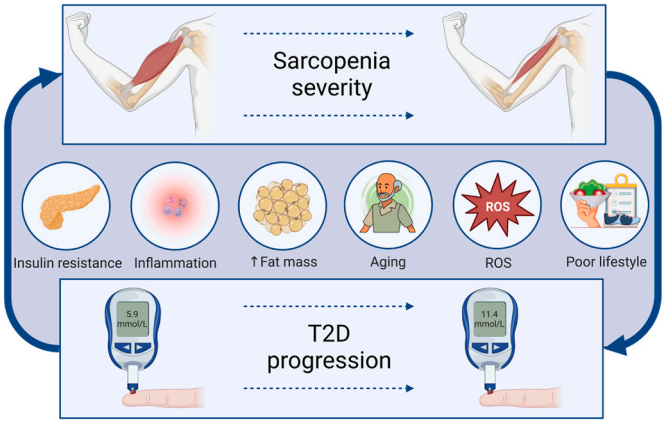

Fig. 2. Interaction between sarcopenia and type 2 diabetes
The combination of factors shown contributes to the development of T2D and sarcopenia while also mutually influencing each other to potentially exacerbate the severity of both conditions. T2D = Type 2 diabetes; ROS= Reactive oxygen species; Poor lifestyle = poor diet and low physical activity level.

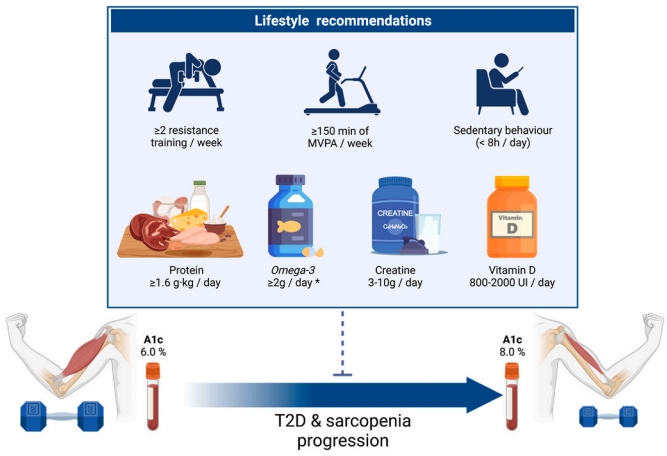

Fig. 3. Lifestyle recommendations for type 2 diabetes and sarcopenia
This figure portrays lifestyle recommendations that carry substantial implications for the development and progression of both sarcopenia and type 2 diabetes. It is to be noted that individuals who performed a higher volume of vigorous-intensity aerobic exercise can attain comparable benefits in terms of glucose control and fitness within a weekly time commitment of less than 150 min; MVPA = Moderate to vigorous physical activity; T2D = Type 2 diabetes; A1c = glycated hemoglobin; * ≥2 Ω 3 (0.16–2.6 g/day of EPA and from 0 to 1.8 g/day of DHA) per day.

In alignment with most organizations and current physical activity guideline recommendations (e.g. Canadian Society for Exercise Physiology; Diabetes Canada; American College of Sports Medicine; World Health Organization), older adults should perform a minimum of two resistance exercise sessions per week to achieve muscle benefits. As proposed by Hurst et al. [83], resistance exercise program design should focus on major muscle groups targeting the whole-body incorporating a variety of repetitions and sets per exercise (Table 1). In addition to muscle, resistance exercise also has the ability to improve glycemic control which may have application for older adults with T2D. For example, a recent meta-analysis including 24 trials (>900 participants) showed a greater reduction in A1c with high-intensity resistance training (≥75% of 1-repetition maximum [1RM]; A1c: 0.61%) compared to low to moderate resistance training (<75% of 1RM; A1c: −0.23% [84]). Collectively, resistance exercise training (≥2 sessions per week), on non-consecutive days, involving large muscle groups and multi-joint exercises should be considered for older adults with and without T2D [85].

4.2. Aerobic training

Although aerobic training (AT) is well known to improve a plethora of health-related parameters in older adults (including VO_2 peak, glycemic control, and blood pressure; [86], AT alone (particularly low-intensity walking) should not be the main priority in the management of sarcopenia [87]. However, despite having a relatively low effect on muscle accretion [88], AT has been shown to improve muscle strength (hand-grip) and functional ability (habitual gait speed) [89,90]. Hand-grip strength and habitual gait speed are strong predictors of health outcomes in older adults (i.e., hospitalization, physical disability; [1,91]. Hand-grip strength is positively associated with whole-body strength [92], an important determinant of gait speed in older adults [1]. For the management of T2D, AT has been shown to successfully reduce A1c, but this improvement also seems to be modulated by exercise volume and intensity [93]. It is therefore not surprising that in the past few decades, various AT modalities manipulating these parameters have emerged, with the majority of focus being on high-intensity interval training (HIIT) and moderate-intensity continuous training

Table 1
General guideline for exercise prescription in older individuals with sarcopenia.

Parameters	Description
Training frequency	• At least two sessions per week [a]
Exercise selection	• Upper and lower body exercise involving major muscle groups (e.i., Bench press, shoulder press, bent over row, squat, leg press, leg curl). [b] • Body weight exercise could be appropriate for individuals with severe sarcopenia. • Incorporating functional movement. [c]
Exercise intensity	• Between 70 and 85% of 1RM. [d, e] • RPE ≥7 (CR10) or between 15 and 18 on the Borg scale (CR20) and close to muscle failure (RIR ≤3).
Exercise volume	• 1–3 sets of 8–12 repetitions, 8–10 major muscle groups.
Rest period	• Between 60 and 90 s for smaller muscle mass or single joint exercises (e.i. Biceps curl). • A longer rest period (≥120 s) for compound movement (e.g., squat) when performed at higher intensities. • At least 48h between sessions.
Variant/ addition	• Incorporating blood flow restriction. [f] •Balance training. [g]

Table inspired by Hurst et al. [83]; Izquierdo et al. [107]; Schoenfeld et al. [143]; 1RM = one repetition maximal; RPE = rate of perceived exertion; RIR = repetition in reserve; CR10 = modified Borg scale.

[a] In individuals with very poor physical capacity could benefit from a single session of RT per week [144], but the primary goal should be a progression towards a higher weakly volume.

[b] The upper body exercise should include movement that required grip strength (e.i. One-arm dumbbell row), which is often needed to perform instrumental tasks.

[c] Incorporating functional strength movements, such as box squats which mimic a weighted sit-to-stand, could also improve the ecological validity and better transferability in real-life settings.

[d] Lower intensity (30–60% 1RM) could generate benefits for people with severe sarcopenia.

[e] Intensity should be introduced in a progressive manner, to 1) learn the appropriate movement technique and 2) to maximize psychological benefits which could have an impact on the compliance and adherence to a given program [145].

[f] Blood flow restriction could also so be a promising alternative to improve muscle mass and strength [146,147], but should be performed under the supervision of a trained exercise physiologist.

[g] Balance training emphasizing static and dynamic stability could reduce the risk of falls.

(MICT). Several meta-analyses have shown no difference between HIIT and MICT in lowering A1c [94–96], while Liu and colleagues (2019) have shown that HIIT may be superior to MICT in improving glycemic control (A1c: −0.37% [−0.55 to −0.19] $P < 0.0001$ [97]). Along those lines, Liubaoerjijin et al. [98], also point out that increasing intensity could generate a greater improvement in glycemic control, confirming the results of a meta-regression previously obtained in one of the first meta-analyses looking at the effect of structured exercise on glycemic control [99]. Taken as a whole, while higher intensity could generate greater improvement in glycemic control, HIIT and MICT appear to provide a similar reduction in A1c in individuals with T2D.

Regarding the acute effect of exercise on glycemic control, when measured with continuous glucose monitoring (CGM), exercise appears to decrease 24h mean glucose by 0.5 [95% CI: −0.7; −0.3] mmol/L ($p < 0.001$; I2 = 73%) in individuals with T2D [100]. Interestingly, meta-regression showed no difference between the type of exercise (HIIT vs. MICT), while the timing of exercise may impact the degree to which an acute bout of exercise influences blood glucose levels over 24 h. Indeed, this meta-analysis found that a single exercise session in the fasting state or in the morning resulted in a significant decrease in 24h blood glucose (−0.7 [−1.1; 0.2] mmol/L; $p = 0.004$ and −0.6 [−0.9; −0.4]; $p < 0.001$, respectively), whereas no decrease was observed when exercise was performed in the afternoon (−0.1 [−0.2; 0.1]; $p = 0.54$).

In addition to the beneficial effect of HIIT and MICT on acute and chronic glycemic control, both exercise modalities have been shown to improve cardiorespiratory fitness (VO_2 peak). Knowing that low cardiorespiratory fitness is more prevalent in individuals with sarcopenia [101] and T2D [102] as well as the close relationship between these variables [102,103], assessing the effect of AT on VO_2 peak is crucial. In individuals with T2D, meta-analyses demonstrate a superior effect of HIIT compared to MICT for improving VO_2 peak [95–97,104]. More recent meta-analyses including 20 studies ($n > 700$ participants) reported an increase of 5.09 mL/kg/min (95% CI = 2.99; 7.19, $I^2 = 80.89$) when HIIT was compared to the control group and 1.9 mL/kg/min (95% CI = 0.81; 2.98, $I^2 = 25.62$) when compared to MICT [96]. The meta-analysis by Wen and colleagues (2019), performed in an adult population without chronic diseases, reported that compared to MICT, only HIIT protocols with long intervals (≥2 min), higher volume at high intensity per session (≥15 min), and medium duration interventions (≥4–12 weeks) generated a superior effect on VO_2 peak [105].

In summary, AT should be prescribed to reach the current exercise guidelines (i.e., ≥150 of moderate to vigorous physical activity per week [106]). Both HIIT and MICT have the potential to improve glycemic control, but higher-intensity aerobic exercise can yield comparable benefits in less time, providing a viable option for individuals with time constraints. Moreover, HIIT appears to improve VO_2 peak to a greater extent compared to MICT, especially when performed with longer duration intervals and a greater amount of time spent at a high intensity per session. Training in the morning may confer greater benefit on 24 h glycemia, but these results require further verification. In addition to these optimizing variables, exercise prescription should also be individualized to one's personal exercise preference (e.g. cycling, running, dancing), medical history, any physical limitations, tolerance, and functional ability [107].

4.3. Daily living activity and sedentary behaviour

In addition to RT and AT, increasing daily living activities and breaking prolonged periods of sedentary time could have significant health impacts [108]. A recent meta-analysis showed that acute interruption of sedentary behaviour with light physical activity could improve glucose homeostasis in patients with T2D [109,110]. Similarly, independent of physical activity level, increasing sedentary behaviour was linked to decreased muscle mass and a higher risk of sarcopenia in community-dwelling older adults [110]. Therefore, in line with the Canadian 24-Hour Movement Guidelines, we recommend older adults at risk or suffering from sarcopenia and T2D, to limit their time spent in sedentary behaviour to 8h per day and to limit recreational screentime at 3h per day [108]. Health care providers should therefore try to implement strategies to break prolonged periods of sedentary behaviours. This could include "exercise snacks", recently defined as short-duration bouts (≤1 min) of vigorous physical exercise, sporadically spread throughout the day, which not only break up sedentary time but may improve VO2 peak and insulin resistance [111]. Therefore, in addition to the current exercise guidelines, these brief bouts of unstructured exercise could be implemented between activities of daily living to positively impact one's cardiometabolic health.

4.4. Nutrition

As previously discussed, T2D is a disturbance in the glucose-insulin axis of metabolism. Therefore, since dietary carbohydrate is the main contributor to high glucose concentration, carbohydrate restriction is an effective intervention to mitigate clinical complications of T2D. Possible benefits of a low-carbohydrate diet for this population include: improved glycemic control, weight management, reduced insulin resistance, lower fat storage (i.e. hepatic, pancreatic, muscle), improved beta-cell function, improved blood pressure, reduced triglyceride levels, and lower inflammation [112–114]. Thus, it is an important nutritional

strategy for people living with T2D, the focus of this review is to explore interventions that ultimately improve muscle health.

4.5. Protein

There is accumulating evidence that older adults with sarcopenia should ingest ~1.6 g kg^{-1}·day^{-1} of protein [11]. Essential amino acids are the primary stimulus of protein synthesis and leucine appears to be the most potent of these amino acids [115]. Further, habitual daily intake of leucine is positively associated with muscle accretion and strength in older adults [116]. Increased habitual dietary intake of protein is effective for improving glycemic control, retaining muscle mass, promoting weight control, reducing inflammation, and increasing insulin sensitivity [117]. Protein ingestion can directly promote post-prandial insulin secretion which may facilitate glucose regulation in older individuals with T2D [118]. Additional benefits are increased muscle protein synthesis, appetite control and satiety [118]. Henceforth, higher protein levels should be encouraged for the aging population with T2D and/or sarcopenia and have potentialized effects in combination with resistance exercise.

4.6. Omega-3 fatty acids

Omega-3 fatty acids may prevent age-related muscle loss by modulating muscle protein kinetics and cell signaling function and oxidative damage linked with inflammation. Most studies have focused on three main types of omega-3 polyunsaturated fatty acids: alpha-linolenic acid (ALA, C18:3 n-3), eicosapentaenoic acid (EPA, C20:5 n-3), and docosahexaenoic acid (DHA, C22:6 n-3) [119]. Randomized controlled trials have shown that omega-3 supplementation stimulates the rates of muscle protein synthesis in older adults [120,121] A recent review concluded that supplementation with omega-3 fatty acids may improve muscle strength and functional ability in older adults [122]. Furthermore, a meta-analysis review showed that omega-3 supplementation had a positive effect on muscle accretion in older adults [123]. In T2D, a systematic review and meta-analysis from randomized clinical trials showed that supplementation with omega-3 had beneficial results on fasting blood glucose and insulin resistance [124]. Some studies propose benefits beyond the latter showing improved lipid profiles, inflammatory mediators [125], and decreasing formation of free radicals [126]. The mechanisms for which omega-3 can positively influence other variables relevant to T2D are not yet fully understood. Some hypotheses include elevated adiponectin levels, lowered proinflammatory cytokines, and reduced nuclear factor-kB (NF-κB) protein expression leading to lower inflammation and improved insulin resistance [125]. Types and doses are not yet totally defined either, with studies ranging from >2g of omega-3, 0.16–2.6 g/day of EPA and from 0 to 1.8 g/day of DHA [119, 123]. More research is needed to confirm the benefits of omega-3 supplementation, alone or in combination with exercise, in sarcopenic older adults with and without T2D.

4.7. Creatine monohydrate

Creatine is an organic compound endogenously produced in the body (liver, brain) or consumed in the diet primarily from red meat and seafood [127] or through commercially manufactured dietary products. Creatine transport into skeletal muscle is elevated if muscle contractions (i.e., resistance exercise) are performed [128]. Several meta-analyses show that the combination of creatine supplementation and resistance exercise improves measures of muscle strength [129–131] and functional ability in older adults [132] compared to resistance exercise training alone. Mechanistically, creatine supplementation may influence high-energy phosphate metabolism, calcium kinetics, glycogen content, muscle protein kinetics, inflammation, and oxidative stress [129,132, 133]. From a T2D perspective, creatine supplementation has the potential to improve glycemic control of skeletal muscle by improving GLUT-4 synthesis [128]. Furthermore, in a randomized, double-blind, placebo-controlled trial, Gualano and colleagues showed that 12 weeks of creatine supplementation (5g per day) combined with resistance exercise training reduced A1c compared to placebo (−1.1% [CI -1.9; −0.4%]; p = 0.004; [134]. Creatine supplementation has the ability to promote changes in glucose homeostasis that may favour a healthier metabolic profile, especially when combine with resistance exercise [135]. However, the efficacy of creatine supplementation, with and without resistance exercise and/or AT, in sarcopenic older adults with T2D is unknown.

4.8. Vitamin D

Vitamin D is a fat-soluble vitamin that can act as a hormone through a nuclear receptor [136] with a dietary reference intake of 600–800UI daily in aging adults [136]. Vitamin D plays a key role in calcium and bone homeostasis and has been linked to sarcopenia and bone metabolism. A recent consensus statement concluded that vitamin D production decreases with age but can be obtained by exposure to UV light [137]. When not possible, individualized supplementation (800-2000UI/day) should be considered for greater muscle strength and improved bone health [138]. However, high dose of vitamin D neither improved indices of obesity, sarcopenia, nor sarcopenic obesity in elderly individuals [139]. Whether supplementation with vitamin D in sarcopenia has beneficial effects such as suppression of muscle atrophy and increased muscle strength is controversial, in part because of the complicated mechanisms underlying the action of vitamin D on muscle tissue [136]. On the other hand, low vitamin D status is highly associated with insulin resistance, impaired insulin secretion, and increased risk of T2D [140]. Therefore, supplementation decreases the risk of progression to T2D among those who are vitamin D deficient [137]. Low vitamin D has also been associated with a number of microvascular and macrovascular complications of T2D including peripheral neuropathy, erectile dysfunction, retinopathy, diabetic kidney disease, and overall mortality [141]. Collectively, maintenance of adequate vitamin D levels is beneficial whilst its supplementation needs better understanding in the context of diabetes and sarcopenia.

5. Clinical relevance and potential limitations

In the context of an aging population where the risk of sarcopenia and T2D is elevated, understanding the bidirectional relationship between these conditions is crucial for optimizing patients' care and health-related outcomes. By implementing lifestyle interventions centered around physical activity and nutrition, healthcare providers can effectively counter the progression of both conditions, ultimately improving the health of the aging population.

The evidence presented in the present review should be interpreted in light of its limitation. Despite that narrative reviews allows a broad overview of a particular topic and are useful in exploring emerging or understudied areas, they could present some bias (e.g., selection bias, incomplete search strategy, and subjective interpretation). Readers are therefore reminded that despite the scientific rigor, the authors' backgrounds, expertise, and interpretations could influence the conclusions of this review. Additionally, the authors also selected, based on the literature, interventions that are more likely to yield significant improvement in both T2D and sarcopenia pathogenesis. Therefore, this does not mean that other interventions or strategies could not lead to improvements in glycemic control or strength.

6. Conclusions and future direction

Past and current research emphasizes that our understanding of the various facets influencing the development of sarcopenia is constantly evolving, which ultimately influences how we can optimally treat and manage this age-related condition. There are common

pathophysiological mechanisms between sarcopenia and T2D. The management and treatment of sarcopenia and T2D are complex and require collaboration across various disciplines. Resistance and aerobic exercise are safe and effective lifestyle interventions for improving musculoskeletal and metabolic health measures in individuals with sarcopenia and T2D. Additional protein, omega-3 fatty acids, creatine monohydrate, and vitamin D all have the potential to provide further benefits, primarily when combined with exercise training.

Declaration of competing interest

D.G.C. has conducted industry-sponsored research involving creatine supplementation and received creatine donations for scientific studies and travel support for presentations involving creatine supplementation at scientific conferences. In addition, D.G.C. serves on the Scientific Advisory Board for Alzchem (a company that manufactures creatine) and as an expert witness/consultant in legal cases involving creatine supplementation.

Acknowledgments

A.M – C was supported by the Frederick Banting and Charles Best scholarship from the Canadian Institutes of Health Research (CIHR). Exercise and nutrition research in J.P.L's laboratory is supported by the Natural Sciences and Engineering Research Council of Canada (RGPIN-2019-05204). Figures were made with Biorender.com.

References

[1] Bhasin S, et al. Sarcopenia definition: the position statements of the sarcopenia definition and outcomes consortium. J Am Geriatr Soc 2020;68(7):1410–8. https://doi.org/10.1111/JGS.16372.
[2] Cawthon PM, et al. Putative cut-points in sarcopenia components and incident adverse health outcomes: an SDOC analysis. J Am Geriatr Soc 2020;68(7): 1429–37. https://doi.org/10.1111/JGS.16517.
[3] Manini TM, Clark BC. Dynapenia and aging: an update. J Gerontol A Biol Sci Med Sci 2012;67(1):28–40. https://doi.org/10.1093/GERONA/GLR010.
[4] Schaap LA, Koster A, Visser M. Adiposity, muscle mass, and muscle strength in relation to functional decline in older persons. Epidemiol Rev 2013;35(1):51–65. https://doi.org/10.1093/EPIREV/MXS006.
[5] Taaffe DR, Henwood TR, Nalls MA, Walker DG, Lang TF, Harris TB. Alterations in muscle attenuation following detraining and retraining in resistance-trained older adults. Gerontology 2009;55(2):217–23. https://doi.org/10.1159/000182084.
[6] Newman AB, et al. Strength, but not muscle mass, is associated with mortality in the health, aging and body composition study cohort. J Gerontol A Biol Sci Med Sci 2006;61(1):72–7. https://doi.org/10.1093/GERONA/61.1.72.
[7] Mitchell WK, Williams J, Atherton P, Larvin M, Lund J, Narici M. Sarcopenia, dynapenia, and the impact of advancing age on human skeletal muscle size and strength; a quantitative review. Front Physiol 2012;3(JUL):28458. https://doi.org/10.3389/FPHYS.2012.00260/BIBTEX.
[8] Goodpaster BH, et al. The loss of skeletal muscle strength, mass, and quality in older adults: the health, aging and body composition study. J Gerontol: Series A 2006;61(10):1059–64. https://doi.org/10.1093/GERONA/61.10.1059.
[9] Anker SD, Morley JE, von Haehling S. Welcome to the ICD-10 code for sarcopenia. J Cachexia Sarcopenia Muscle 2016;7(5):512–4. https://doi.org/10.1002/JCSM.12147.
[10] Cruz-Jentoft AJ, et al. Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing 2019;48(1):16–31. https://doi.org/10.1093/AGEING/AFY169.
[11] Coletta G, Phillips SM. An elusive consensus definition of sarcopenia impedes research and clinical treatment: a narrative review. Ageing Res Rev 2023;86: 101883. https://doi.org/10.1016/J.ARR.2023.101883.
[12] Shou J, Chen PJ, Xiao WH. Mechanism of increased risk of insulin resistance in aging skeletal muscle. Diabetol Metab Syndrome 2020;12(1). https://doi.org/10.1186/S13098-020-0523-X.
[13] Mesinovic J, Zengin A, De Courten B, Ebeling PR, Scott D. Sarcopenia and type 2 diabetes mellitus: a bidirectional relationship. Diabetes Metab Syndr Obes 2019; 12:1057–72. https://doi.org/10.2147/DMSO.S186600.
[14] Brown JC, Harhay MO, Harhay MN. Sarcopenia and mortality among a population-based sample of community-dwelling older adults. J Cachexia Sarcopenia Muscle 2016;7(3):290–8. https://doi.org/10.1002/JCSM.12073.
[15] Salehidoost R, Mansouri A, Amini M, Aminorroaya Yamini S, Aminorroaya A. Diabetes and all-cause mortality, a 18-year follow-up study. Scientific Reports 2020 10:1 2020;10(1):1–8. https://doi.org/10.1038/s41598-020-60142-y.
[16] Huang LT, Wang JH. The therapeutic intervention of sex steroid hormones for sarcopenia. Front Med 2021;8:739251. https://doi.org/10.3389/FMED.2021.739251.
[17] Dalle S, Rossmeislova L, Koppo K. The role of inflammation in age-related sarcopenia. Front Physiol 2017;8. https://doi.org/10.3389/FPHYS.2017.01045. DEC.
[18] McKinnon NB, Connelly DM, Rice CL, Hunter SW, Doherty TJ. Neuromuscular contributions to the age-related reduction in muscle power: mechanisms and potential role of high velocity power training. Ageing Res Rev 2017;35:147–54. https://doi.org/10.1016/J.ARR.2016.09.003.
[19] Wiedmer P, et al. Sarcopenia – molecular mechanisms and open questions. Ageing Res Rev 2021;65:101200. https://doi.org/10.1016/J.ARR.2020.101200.
[20] Paulussen KJM, McKenna CF, Beals JW, Wilund KR, Salvador AF, Burd NA. Anabolic resistance of muscle protein turnover comes in various shapes and sizes. Front Nutr 2021;8:115. https://doi.org/10.3389/FNUT.2021.615849/BIBTEX.
[21] Clark BC, Carson RG. Sarcopenia and neuroscience: learning to communicate. J Gerontol: Series A 2021;76(10):1882–90. https://doi.org/10.1093/GERONA/GLAB098.
[22] Larsson L, et al. Sarcopenia: aging-related loss of muscle mass and function. Physiol Rev 2019;99(1):427–511. https://doi.org/10.1152/PHYSREV.00061.2017/ASSET/IMAGES/LARGE/Z9J0041828880019 [JPEG].
[23] Khosa S, Trikamji B, Khosa GS, Khanli HM, Mishra SK. An overview of neuromuscular junction aging findings in human and animal studies. Curr Aging Sci 2019;12(1):28–34. https://doi.org/10.2174/1874609812666190603165746.
[24] Kalyani RR, Corriere M, Ferrucci L. Age-related and disease-related muscle loss: the effect of diabetes, obesity, and other diseases. Lancet Diabetes Endocrinol 2014;2(10):819. https://doi.org/10.1016/S2213-8587(14)70034-8.
[25] 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 2021;13(1):183. https://doi.org/10.3390/NU13010183. Vol. 13, *Page 183*.
[26] Nolan CJ, Damm P, Prentki M. Type 2 diabetes across generations: from pathophysiology to prevention and management. Lancet 2011;378(9786): 169–81. https://doi.org/10.1016/S0140-6736(11)60614-4.
[27] Merz KE, Thurmond DC. Role of skeletal muscle in insulin resistance and glucose uptake. Compr Physiol 2020;10(3):785. https://doi.org/10.1002/CPHY.C190029.
[28] Halim M, Halim A. The effects of inflammation, aging and oxidative stress on the pathogenesis of diabetes mellitus (type 2 diabetes). Diabetes Metabol Syndr: Clin Res Rev 2019;13(2):1165–72. https://doi.org/10.1016/J.DSX.2019.01.040.
[29] B JE, Srikanth Bellary CJB, Kyrou Ioannis. Type 2 diabetes mellitus in older adults: clinical considerations and management. Nat Rev Endocrinol 2021;17: 534–48. https://doi.org/10.1038/s41574-021-00512-2.
[30] Zamboni M, Mazzali G, Fantin F, Rossi A, Di Francesco V. Sarcopenic obesity: a new category of obesity in the elderly. Nutr Metabol Cardiovasc Dis 2008;18(5): 388–95. https://doi.org/10.1016/J.NUMECD.2007.10.002.
[31] Giha HA, Alamin OAO, Sater MS. Diabetic sarcopenia: metabolic and molecular appraisal. Acta Diabetol 2022;59(8):989–1000. https://doi.org/10.1007/S00592-022-01883-2/FIGURES/3.
[32] DeFronzo RA, Tripathy D. Skeletal muscle insulin resistance is the primary defect in type 2 diabetes. suppl_2 Diabetes Care 2009;32:S157–63. https://doi.org/10.2337/DC09-S302.
[33] Beaudry KM, Devries MC. Nutritional strategies to combat type 2 diabetes in aging adults: the importance of protein. Front Nutr 2019;6:138. https://doi.org/10.3389/FNUT.2019.00138/BIBTEX.
[34] Scott D, de Courten B, Ebeling PR. Sarcopenia: a potential cause and consequence of type 2 diabetes in Australia's ageing population? Med J Aust 2016;205(7): 329–33. https://doi.org/10.5694/MJA16.00446.
[35] Sugimoto K, et al. Hyperglycemia in non-obese patients with type 2 diabetes is associated with low muscle mass: the Multicenter Study for Clarifying Evidence for Sarcopenia in Patients with Diabetes Mellitus. J Diabetes Investig 2019;10(6): 1471–9. https://doi.org/10.1111/JDI.13070.
[36] Rehunen SKJ, Kautiainen H, Korhonen PE, Eriksson JG. A high lean body mass is not protecting from type 2 diabetes in the presence of a high body fat mass. Diabetes Metab 2021;47(6). https://doi.org/10.1016/J.DIABET.2020.101219.
[37] Mesinovic J, McMillan LB, Shore-Lorenti C, De Courten B, Ebeling PR, Scott D. Metabolic syndrome and its associations with components of sarcopenia in overweight and obese older adults. J Clin Med 2019;8(2). https://doi.org/10.3390/JCM8020145.
[38] Lagacé JC, Marcotte-Chenard A, Paquin J, Tremblay D, Brochu M, Dionne IJ. Increased odds of having the metabolic syndrome with greater fat-free mass: counterintuitive results from the National Health and Nutrition Examination Survey database. J Cachexia Sarcopenia Muscle 2022;13(1):377–85. https://doi.org/10.1002/JCSM.12856.
[39] Chaudhuri J, et al. The role of advanced glycation end products in aging and metabolic diseases: bridging association and causality. Cell Metabol 2018;28(3): 337–52. https://doi.org/10.1016/J.CMET.2018.08.014.
[40] Khamseh ME, Malek M, Aghili R, Emami Z. Sarcopenia and diabetes: pathogenesis and consequences 2011;11(5):230–4. https://doi.org/10.1177/1474651411413644. 10.1177/1474651411413644.
[41] Cui M, et al. A cross-sectional study: associations between sarcopenia and clinical characteristics of patients with type 2 diabetes. Medicine 2020;99(2). https://doi.org/10.1097/MD.0000000000018708.
[42] Volpi E, Nazemi R, Fujita S. Muscle tissue changes with aging. Curr Opin Clin Nutr Metab Care 2004;7(4):405. https://doi.org/10.1097/01.MCO.0000134362.76653.B2.
[43] Sachs S, et al. Intermuscular adipose tissue directly modulates skeletal muscle insulin sensitivity in humans. Am J Physiol Endocrinol Metab 2019;316(5): E866–79. https://doi.org/10.1152/AJPENDO.00243.2018/ASSET/IMAGES/LARGE/ZH10021980320007 [JPEG].

[44] Goodpaster BH, Thaete FL, Kelley DE. Thigh adipose tissue distribution is associated with insulin resistance in obesity and in type 2 diabetes mellitus. Am J Clin Nutr 2000;71(4):885–92. https://doi.org/10.1093/AJCN/71.4.885.

[45] Yu F, Fan Y, Sun H, Li T, Dong Y, Pan S. Intermuscular adipose tissue in Type 2 diabetes mellitus: non-invasive quantitative imaging and clinical implications. Diabetes Res Clin Pract 2022;187:109881. https://doi.org/10.1016/J.DIABRES.2022.109881.

[46] Kahn D, et al. Quantifying the inflammatory secretome of human intermuscular adipose tissue. Phys Rep Aug. 2022;10(16):e15424. https://doi.org/10.14814/PHY2.15424.

[47] Cleasby ME, Jamieson PM, Atherton PJ. Insulin resistance and sarcopenia: mechanistic links between common co-morbidities. J Endocrinol 2016;229(2):R67–81. https://doi.org/10.1530/JOE-15-0533.

[48] Abbatecola AM, et al. Insulin resistance and muscle strength in older persons. J Gerontol: Series A 2005;60(10):1278–82. https://doi.org/10.1093/GERONA/60.10.1278.

[49] Perry BD, et al. Muscle atrophy in patients with Type 2 Diabetes Mellitus: roles of inflammatory pathways, physical activity and exercise. Exerc Immunol Rev 2016;22:94.

[50] Sayer AA, Dennison EM, Syddall HE, Gilbody HJ, Phillips DIW, Cooper C. Type 2 diabetes, muscle strength, and impaired physical FunctionThe tip of the iceberg? Diabetes Care 2005;28(10):2541–2. https://doi.org/10.2337/DIACARE.28.10.2541.

[51] Addison O, Marcus RL, Lastayo PC, Ryan AS. Intermuscular fat: a review of the consequences and causes. Internet J Endocrinol 2014;2014. https://doi.org/10.1155/2014/309570.

[52] A Kalinkovich GL. Sarcopenic obesity or obese sarcopenia: a cross talk between age-associated adipose tissue and skeletal muscle inflammation as a main mechanism of the pathogenesis. Ageing Res Rev 2017;35:200–21. https://doi.org/10.1016/j.arr.2016.09.008.

[53] Sachs S, et al. Intermuscular adipose tissue directly modulates skeletal muscle insulin sensitivity in humans. Am J Physiol Endocrinol Metab 2019;316(5):E866. https://doi.org/10.1152/AJPENDO.00243.2018.

[54] Yu F, Fan Y, Sun H, Li T, Dong Y, Pan S. Intermuscular adipose tissue in Type 2 diabetes mellitus: non-invasive quantitative imaging and clinical implications. Diabetes Res Clin Pract 2022;187:109881. https://doi.org/10.1016/J.DIABRES.2022.109881.

[55] Rong YD, Bian AL, Hu HY, Ma Y, Zhou XZ. Study on relationship between elderly sarcopenia and inflammatory cytokine IL-6, anti-inflammatory cytokine IL-10. BMC Geriatr 2018;18(1):1–6. https://doi.org/10.1186/S12877-018-1007-9/TABLES/4.

[56] Pan L, et al. Inflammation and sarcopenia: a focus on circulating inflammatory cytokines. Exp Gerontol 2021;154:111544. https://doi.org/10.1016/J.EXGER.2021.111544.

[57] Gomes MJ, et al. Skeletal muscle aging: influence of oxidative stress and physical exercise. Oncotarget 2017;8(12):20428. https://doi.org/10.18632/ONCOTARGET.14670.

[58] Oguntibeju OO. Type 2 diabetes mellitus, oxidative stress and inflammation: examining the links. Int J Physiol Pathophysiol Pharmacol 2019;11(3):45.

[59] Hesselink MKC, Schrauwen-Hinderling V, Schrauwen P. Skeletal muscle mitochondria as a target to prevent or treat type 2 diabetes mellitus. Nature Reviews Endocrinology 2016 12:11 2016;12(11):633–45. https://doi.org/10.1038/nrendo.2016.104.

[60] Qiu MG, Zhu XH. Aging changes of the angioarchitecture and arterial morphology of the spinal cord in rats. Gerontology 2004;50(6):360–5. https://doi.org/10.1159/000080173.

[61] Abbott CA, et al. The North-West Diabetes Foot Care Study: incidence of, and risk factors for, new diabetic foot ulceration in a community-based patient cohort. Diabet Med 2002;19(5):377–84. https://doi.org/10.1046/J.1464-5491.2002.00698.X.

[62] Davies M, Brophy S, Williams R, Taylor A. The prevalence, severity, and impact of painful diabetic peripheral neuropathy in type 2 diabetes. Diabetes Care 2006;29(7):1518–22. https://doi.org/10.2337/DC05-2228.

[63] Nomura T, Ishiguro T, Ohira M, Ikeda Y. Diabetic polyneuropathy is a risk factor for decline of lower extremity strength in patients with type 2 diabetes. J Diabetes Investig 2018;9(1):186–92. https://doi.org/10.1111/JDI.12658.

[64] Strotmeyer ES, et al. The relationship of reduced peripheral nerve function and diabetes with physical performance in older white and black adults: the health, aging, and body composition (health ABC) study. Diabetes Care 2008;31(9):1767. https://doi.org/10.2337/DC08-0433.

[65] Fukuda T, et al. Association of diabetic retinopathy with both sarcopenia and muscle quality in patients with type 2 diabetes: a cross-sectional study. BMJ Open Diabetes Res Care 2017;5(1):e000404. https://doi.org/10.1136/BMJDRC-2017-000404.

[66] Wang XH, Mitch WE. Mechanisms of muscle wasting in chronic kidney disease. Nature Reviews Nephrology 2014 10:9 2014;10(9):504–16. https://doi.org/10.1038/nrneph.2014.112.

[67] Groen BBL, et al. Skeletal muscle capillary density and microvascular function are compromised with aging and type 2 diabetes. J Appl Physiol 2014;116(8):998–1005. https://doi.org/10.1152/JAPPLPHYSIOL.00919.2013/ASSET/IMAGES/LARGE/ZDG0091410190004 [JPEG].

[68] Soyoye DO, Abiodun OO, Ikem RT, Kolawole BA, Akintomide AO. Diabetes and peripheral artery disease: a review. World J Diabetes 2021;12(6):827. https://doi.org/10.4239/WJD.V12.I6.827.

[69] Dziubek W, et al. Peripheral arterial disease decreases muscle torque and functional walking capacity in elderly. Maturitas 2015;81(4):480–6. https://doi.org/10.1016/J.MATURITAS.2015.06.001.

[70] McDermott MM. Lower extremity manifestations of peripheral artery disease: the pathophysiologic and functional implications of leg ischemia. Circ Res 2015;116(9):1540–50. https://doi.org/10.1161/CIRCRESAHA.114.303517.

[71] Heikkilä K, Coughlin PA, Pentti J, Kivimäki M, Halonen JI. Physical activity and peripheral artery disease: two prospective cohort studies and a systematic review. Atherosclerosis 2019;286:114–20. https://doi.org/10.1016/j.atherosclerosis.2019.05.008.

[72] Ogama N, et al. Association of glucose fluctuations with sarcopenia in older adults with type 2 diabetes mellitus. Journal of Clinical Medicine 2019 2019;8(3):319. https://doi.org/10.3390/JCM8030319. Vol. 8, *Page 319*.

[73] 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 2021;10(8):1958. https://doi.org/10.3390/CELLS10081958. Vol. 10, Page 1958.

[74] Chen F, et al. Risk factors for sarcopenia in the elderly with type 2 diabetes mellitus and the effect of metformin. J Diabetes Res 2020;2020. https://doi.org/10.1155/2020/3950404.

[75] Rizzo MR, et al. Sarcopenia in elderly diabetic patients: role of dipeptidyl peptidase 4 inhibitors. J Am Med Dir Assoc 2016;17(10):896–901. https://doi.org/10.1016/J.JAMDA.2016.04.016.

[76] Dent E, et al. International clinical practice guidelines for sarcopenia (ICFSR): screening, diagnosis and management. J Nutr Health Aging 2018;22(10):1148–61. https://doi.org/10.1007/S12603-018-1139-9/METRICS.

[77] Chen N, He X, Feng Y, Ainsworth BE, Liu Y. Effects of resistance training in healthy older people with sarcopenia: a systematic review and meta-analysis of randomized controlled trials. European Review of Aging and Physical Activity 2021;18(1):23. https://doi.org/10.1186/S11556-021-00277-7.

[78] Hughes MA, Myers BS, Schenkman ML. The role of strength in rising from a chair in the functionally impaired elderly. J Biomech 1996;29(12):1509–13. https://doi.org/10.1016/S0021-9290(96)80001-7.

[79] Ploutz-Snyder LL, Manini T, Ploutz-Snyder RJ, Wolf DA. Functionally relevant thresholds of quadriceps femoris strength. J Gerontol A Biol Sci Med Sci 2002;57(4):B144–52. https://doi.org/10.1093/GERONA/57.4.B144.

[80] Peterson MD, Rhea MR, Sen A, Gordon PM. Resistance exercise for muscular strength in older adults: a meta-analysis. Ageing Res Rev 2010;9(3):226. https://doi.org/10.1016/J.ARR.2010.03.004.

[81] Vlietstra L, Hendrickx W, Waters DL. Exercise interventions in healthy older adults with sarcopenia: a systematic review and meta-analysis. Australas J Ageing 2018;37(3):169–83. https://doi.org/10.1111/AJAG.12521.

[82] Talar K, Hernández-belmonte A, Vetrovsky T, Steffl M, Kałamacka E, Courel-ibáñez J. Benefits of resistance training in early and late stages of frailty and sarcopenia: a systematic review and meta-analysis of randomized controlled studies. Journal of Clinical Medicine 2021 2021;10(8):1630. https://doi.org/10.3390/JCM10081630. Vol. 10, *Page 1630*.

[83] Hurst C, et al. Resistance exercise as a treatment for sarcopenia: prescription and delivery. Age Ageing 2022;51(2):1–10. https://doi.org/10.1093/AGEING/AFAC003.

[84] Liu Y, Ye W, Chen Q, Zhang Y, Kuo CH, Korivi M. Resistance exercise intensity is correlated with attenuation of HbA1c and insulin in patients with type 2 diabetes: a systematic review and meta-analysis. Int J Environ Res Publ Health 2019;16(1). https://doi.org/10.3390/IJERPH16010140.

[85] Mendes R, et al. Exercise prescription for patients with type 2 diabetes-a synthesis of international recommendations: narrative review. Br J Sports Med 2016;50(22):1379–81. https://doi.org/10.1136/BJSPORTS-2015-094895.

[86] Bouaziz W, Vogel T, Schmitt E, Kaltenbach G, Geny B, Lang PO. Health benefits of aerobic training programs in adults aged 70 and over: a systematic review. Arch Gerontol Geriatr 2017;69:110–27. https://doi.org/10.1016/J.ARCHGER.2016.10.012.

[87] Barajas-Galindo DE, González Arnáiz E, Ferrero Vicente P, Ballesteros-Pomar MD. Effects of physical exercise in sarcopenia. A systematic review. Endocrinol Diabetes Nutr 2021;68(3):159–69. https://doi.org/10.1016/J.ENDINU.2020.02.010.

[88] Sultana RN, Sabag A, Keating SE, Johnson NA. The effect of low-volume high-intensity interval training on body composition and cardiorespiratory fitness: a systematic review and meta-analysis. Springer International Publishing Sports Med 2019;49(11):1687–721. https://doi.org/10.1007/s40279-019-01167-w.

[89] Henderson RM, et al. Gait speed response to aerobic versus resistance exercise training in older adults. Aging Clin Exp Res 2017;29(5):969–76. https://doi.org/10.1007/S40520-016-0632-4.

[90] Bao W, et al. Exercise programs for muscle mass, muscle strength and physical performance in older adults with sarcopenia: a systematic review and meta-analysis. Aging Dis 2020;11(4):863. https://doi.org/10.14336/AD.2019.1012.

[91] Kirk B, Zanker J, Bani Hassan E, Bird S, Brennan-Olsen S, Duque G. Sarcopenia definitions and outcomes consortium (SDOC) criteria are strongly associated with malnutrition, depression, falls, and fractures in high-risk older persons. J Am Med Dir Assoc 2021;22(4):741–5. https://doi.org/10.1016/J.JAMDA.2020.06.050.

[92] Bohannon RW. Muscle strength: clinical and prognostic value of hand-grip dynamometry. Curr Opin Clin Nutr Metab Care 2015;18(5):465–70. https://doi.org/10.1097/MCO.0000000000000202.

[93] Delevatti RS, et al. The role of aerobic training variables progression on glycemic control of patients with type 2 diabetes: a systematic review with meta-analysis. Sports Med Open 2019;5(1):1–17. https://doi.org/10.1186/S40798-019-0194-Z/TABLES/5.

[94] Jelleyman C, et al. The effects of high-intensity interval training on glucose regulation and insulin resistance: a meta-analysis. Obes Rev 2015;16(11):942–61. https://doi.org/10.1111/obr.12317.
[95] de Nardi AT, Tolves T, Lenzi TL, Signori LU, da Silva AMV. High-intensity interval training versus continuous training on physiological and metabolic variables in prediabetes and type 2 diabetes: a meta-analysis. Diabetes Res Clin Pract 2018; 137(2018):149–59. https://doi.org/10.1016/j.diabres.2017.12.017.
[96] de Mello MB, Righi NC, Schuch FB, Signori LU, da Silva AMV. Effect of high-intensity interval training protocols on VO2max and HbA1c level in people with type 2 diabetes: a systematic review and meta-analysis. Ann Phys Rehabil Med 2022;65(5):101586. https://doi.org/10.1016/J.REHAB.2021.101586.
[97] Liu J-X, et al. Effectiveness of high-intensity interval training on glycemic control and cardiorespiratory fitness in patients with type 2 diabetes: a systematic review and meta-analysis. Springer International Publishing Aging Clin Exp Res 2019;31 (5):575–93. https://doi.org/10.1007/s40520-018-1012-z.
[98] Liubaoerjijin Y, Terada T, Fletcher K, Boulé NG. Effect of aerobic exercise intensity on glycemic control in type 2 diabetes: a meta-analysis of head-to-head randomized trials. Acta Diabetol 2016;53(5):769–81. https://doi.org/10.1007/s00592-016-0870-0.
[99] Boulé NG, et al. Meta-analysis of the effect of structured exercise training on cardiorespiratory fitness in Type 2 diabetes mellitus. Diabetologia 2003;46(8): 1071–81. https://doi.org/10.1007/s00125-003-1160-2.
[100] Munan M, et al. Acute and chronic effects of exercise on continuous glucose monitoring outcomes in type 2 diabetes: a meta-analysis. Front Endocrinol 2020; 11:495. https://doi.org/10.3389/fendo.2020.00495.
[101] Chien MY, Kuo HK, Wu YT. Sarcopenia, cardiopulmonary fitness, and physical disability in community-dwelling elderly people. Phys Ther 2010;90(9):1277–87. https://doi.org/10.2522/PTJ.20090322.
[102] Abushamat LA, et al. Mechanistic causes of reduced cardiorespiratory fitness in type 2 diabetes. J Endocr Soc 2020;4(7):1–15. https://doi.org/10.1210/JENDSO/BVAA063.
[103] Fleg JL, Lakatta EG. Role of muscle loss in the age-associated reduction in VO2 max. J Appl Physiol 1988;65(3):1147–51. https://doi.org/10.1152/JAPPL.1988.65.3.1147.
[104] Lora-Pozo, et al. Anthropometric, cardiopulmonary and metabolic benefits of the high-intensity interval training versus moderate, low-intensity or control for type 2 diabetes: systematic review and meta-analysis. Int J Environ Res Publ Health 2019;16(22):4524. https://doi.org/10.3390/ijerph16224524.
[105] Wen D, et al. Effects of different protocols of high intensity interval training for VO2max improvements in adults: a meta-analysis of randomised controlled trials. J Sci Med Sport 2019;22(8):941–7. https://doi.org/10.1016/J.JSAMS.2019.01.013.
[106] Sigal RJ, et al. Physical activity and diabetes. Can J Diabetes 2018;42:S54–63. https://doi.org/10.1016/j.jcjd.2017.10.008.
[107] Izquierdo M, et al. International exercise recommendations in older adults (ICFSR): expert consensus guidelines. J Nutr Health Aging 2021;25(7):824–53. https://doi.org/10.1007/S12603-021-1665-8.
[108] Ross R, et al. Canadian 24-Hour Movement Guidelines for Adults aged 18-64 years and Adults aged 65 years or older: an integration of physical activity, sedentary behaviour, and sleep. Suppl. 2 Appl Physiol Nutr Metabol 2020;45(10): S57–102. https://doi.org/10.1139/APNM-2020-0467.
[109] García León D, Trujillo Gittermann LM, Soto Isla N, Villanueva Boratovic SR, von Oetinger Giacoman A. Effects of break in sedentary behaviour on blood glucose control in diabetic patients. Systematic review. Endocrinol Diabetes Nutr 2022;69 (10):888–96. https://doi.org/10.1016/J.ENDIEN.2022.11.027.
[110] Gianoudis J, Bailey CA, Daly RM. Associations between sedentary behaviour and body composition, muscle function and sarcopenia in community-dwelling older adults. Osteoporos Int 2015;26(2):571–9. https://doi.org/10.1007/S00198-014-2895-Y.
[111] Islam H, Gibala MJ, Little JP. Exercise snacks: a novel strategy to improve cardiometabolic health. Exerc Sport Sci Rev 2022;50(1):31–7. https://doi.org/10.1249/JES.0000000000000275.
[112] Nielsen JV, Joensson EA. Low-carbohydrate diet in type 2 diabetes: stable improvement of bodyweight and glycemic control during 44 months follow-up. Nutr Metab 2008;5(1):1–6. https://doi.org/10.1186/1743-7075-5-14/TABLES/2.
[113] Hansen CD, et al. Effect of calorie-unrestricted low-carbohydrate, high-fat diet versus high-carbohydrate, low-fat diet on type 2 diabetes and nonalcoholic fatty liver disease : a randomized controlled trial. Ann Intern Med 2023;176(1):10–21. https://doi.org/10.7326/M22-1787.
[114] Wheatley SD, Deakin TA, Arjomandkhah NC, Hollinrake PB, Reeves TE. Low carbohydrate dietary approaches for people with type 2 diabetes—a narrative review. Front Nutr 2021;8:687658. https://doi.org/10.3389/FNUT.2021.687658/BIBTEX.
[115] Morley JE, et al. Nutritional recommendations for the management of sarcopenia. J Am Med Dir Assoc 2010;11(6):391–6. https://doi.org/10.1016/J.JAMDA.2010.04.014.
[116] Lixandrão ME, et al. Daily leucine intake is positively associated with lower limb skeletal muscle mass and strength in the elderly. Nutrients 2021;13(10). https://doi.org/10.3390/NU13103536.
[117] Millward DJ, Layman DK, Tomé D, Schaafsma G. Protein quality assessment: impact of expanding understanding of protein and amino acid needs for optimal health. Am J Clin Nutr 2008;87(5):1576S–81S. https://doi.org/10.1093/AJCN/87.5.1576S.
[118] Lewgood J, et al. Efficacy of dietary and supplementation interventions for individuals with type 2 diabetes. Nutrients 2021;13(7). https://doi.org/10.3390/NU13072378.
[119] Huang YH, Chiu WC, Hsu YP, Lo YL, Wang YH. Effects of omega-3 fatty acids on muscle mass, muscle strength and muscle performance among the elderly: a meta-analysis. Nutrients 2020 2020;12(12):3739. https://doi.org/10.3390/NU12123739. Vol. 12, *Page 3739*.
[120] Smith GI, et al. Dietary omega-3 fatty acid supplementation increases the rate of muscle protein synthesis in older adults: a randomized controlled trial. Am J Clin Nutr 2011;93(2):402–12. https://doi.org/10.3945/AJCN.110.005611.
[121] Smith GI, Julliand S, Reeds DN, Sinacore DR, Klein S, Mittendorfer B. Fish oil-derived n-3 PUFA therapy increases muscle mass and function in healthy older adults. Am J Clin Nutr 2015;102(1):115–22. https://doi.org/10.3945/AJCN.114.105833.
[122] Cornish SM, et al. Effects of omega-3 supplementation alone and combined with resistance exercise on skeletal muscle in older adults: a systematic review and meta-analysis. Nutrients 2022 2022;14(11):2221. https://doi.org/10.3390/NU14112221. Vol. 14, *Page 2221*.
[123] Bird JK, Troesch B, Warnke I, Calder PC. The effect of long chain omega-3 polyunsaturated fatty acids on muscle mass and function in sarcopenia: a scoping systematic review and meta-analysis. Clin Nutr ESPEN 2021;46:73–86. https://doi.org/10.1016/J.CLNESP.2021.10.011.
[124] Delpino FM, et al. Omega-3 supplementation and diabetes: A systematic review and meta-analysis 2021;62(16):4435–48. https://doi.org/10.1080/10408398.2021.1875977. 10.1080/10408398.2021.1875977.
[125] Natto ZS, Yaghmoor W, Alshaeri HK, Van Dyke TE. Omega-3 fatty acids effects on inflammatory biomarkers and lipid profiles among diabetic and cardiovascular disease patients: a systematic review and meta-analysis. Scientific Reports 2019 9: 1 2019;9(1):1–10. https://doi.org/10.1038/s41598-019-54535-x.
[126] Behl T, et al. Role of omega-3-fatty acids in the management of diabetes and associated complications. Bioactive Food as Dietary Interventions for Diabetes 2019:185–92. https://doi.org/10.1016/B978-0-12-813822-9.00012-6.
[127] Wyss M, Kaddurah-Daouk R. Creatine and creatinine metabolism. Physiol Rev 2000;80(3):1107–213. https://doi.org/10.1152/PHYSREV.2000.80.3.1107.
[128] Op 'T Eijnde B, Richter EA, Henquin JC, Kiens B, Hespel P. Effect of creatine supplementation on creatine and glycogen content in rat skeletal muscle. Acta Physiol Scand 2001;171(2):169–76. https://doi.org/10.1046/J.1365-201X.2001.00786.X.
[129] Chilibeck PD, Kaviani M, Candow DG, Zello GA. Effect of creatine supplementation during resistance training on lean tissue mass and muscular strength in older adults: a meta-analysis. Open Access J Sports Med 2017;8:213. https://doi.org/10.2147/OAJSM.S123529.
[130] Forbes SC, Candow DG, Ostojic SM, Roberts MD, Chilibeck PD. Meta-analysis examining the importance of creatine ingestion strategies on lean tissue mass and strength in older adults. Nutrients 2021;13(6). https://doi.org/10.3390/NU13061912/S1.
[131] Devries MC, Phillips SM. Creatine supplementation during resistance training in older adults-a meta-analysis. Med Sci Sports Exerc 2014;46(6):1194–203. https://doi.org/10.1249/MSS.0000000000000220.
[132] Candow DG, Forbes SC, Chilibeck PD, Cornish SM, Antonio J, Kreider RB. Effectiveness of creatine supplementation on aging muscle and bone: focus on falls prevention and inflammation. J Clin Med 2019;8(4). https://doi.org/10.3390/JCM8040488.
[133] Candow DG, Chilibeck PD, Forbes SC, Fairman CM, Gualano B, Roschel H. Creatine supplementation for older adults: focus on sarcopenia, osteoporosis, frailty and Cachexia. Bone 2022;162. https://doi.org/10.1016/j.bone.2022.116467.
[134] Gualano B, et al. Creatine in type 2 diabetes: a randomized, double-blind, placebo-controlled trial. Med Sci Sports Exerc 2011;43(5):770–8. https://doi.org/10.1249/MSS.0B013E3181FCEE7D.
[135] Solis MY, Artioli GG, Gualano B. Potential of creatine in glucose management and diabetes. Nutrients 2021 2021;13(2):570. https://doi.org/10.3390/NU13020570. Vol. 13, *Page 570*.
[136] Uchitomi R, Oyabu M, Kamei Y. Vitamin D and sarcopenia: potential of vitamin D supplementation in sarcopenia prevention and treatment. Nutrients 2020 2020;12 (10):3189. https://doi.org/10.3390/NU12103189. Vol. 12, *Page 3189*.
[137] Giustina A, et al. Vitamin D in the older population: a consensus statement. Endocrine 2022;79(1):31–44. https://doi.org/10.1007/S12020-022-03208-3/FIGURES/2.
[138] Dawson-Hughes B, et al. IOF position statement: vitamin D recommendations for older adults. Osteoporos Int 2010;21(7):1151–4. https://doi.org/10.1007/S00198-010-1285-3.
[139] Jabbour J, Rahme M, Mahfoud ZR, El-Hajj Fuleihan G. Effect of high dose vitamin D supplementation on indices of sarcopenia and obesity assessed by DXA among older adults: a randomized controlled trial. Endocrine 2022;76(1):162–71. https://doi.org/10.1007/S12020-021-02951-3/TABLES/3.
[140] Szymczak-Pajor I, Śliwińska A. Analysis of association between vitamin D deficiency and insulin resistance. Nutrients 2019;11(4). https://doi.org/10.3390/NU11040794.
[141] Sacerdote A, Dave P, Lokshin V, Bahtiyar G. Type 2 diabetes mellitus, insulin resistance, and vitamin D. Curr Diabetes Rep 2019;19(10):1–12. https://doi.org/10.1007/S11892-019-1201-Y/TABLES/2.
[142] Falkenhain K, Islam H, Little p J. Exogenous ketone supplementation: an emerging tool for physiologists with potential as a metabolic therapy. Front Nutr 2022. In press.
[143] Schoenfeld BJ, et al. Resistance training recommendations to maximize muscle hypertrophy in an athletic population: position stand of the IUSCA. International Journal of Strength and Conditioning 2021;1(1). https://doi.org/10.47206/IJSC.V1I1.81.

[144] Taaffe DR, Duret C, Wheeler S, Marcus R. Once-weekly resistance exercise improves muscle strength and neuromuscular performance in older adults. J Am Geriatr Soc 1999;47(10):1208–14. https://doi.org/10.1111/J.1532-5415.1999.TB05201.X.

[145] Bibeau WS, Moore JB, Mitchell NG, Vargas-Tonsing T, Bartholomew JB. Effects of acute resistance training of different intensities and rest periods on anxiety and affect. J Strength Condit Res 2010;24(8):2184–91. https://doi.org/10.1519/JSC.0B013E3181AE794B.

[146] Hughes L, Paton B, Rosenblatt B, Gissane C, Patterson SD. Blood flow restriction training in clinical musculoskeletal rehabilitation: a systematic review and meta-analysis. Br J Sports Med 2017;51(13):1003–11. https://doi.org/10.1136/BJSPORTS-2016-097071.

[147] Centner C, Wiegel P, Gollhofer A, König D. Effects of blood flow restriction training on muscular strength and hypertrophy in older individuals: a systematic review and meta-analysis. Sports Med 2019;49(1):95–108. https://doi.org/10.1007/S40279-018-0994-1/FIGURES/6.