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Sarcopenia, malnutrition, and frailty: disease implications for geriatric DM patients

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1. RECOMMENDATIONS

A. Due to the risk of sarcopenia, the treatment of DM in geriatric patients should be individualized according to the patient's characteristics, associated comorbidities, and DM complications, which may increase the risk of sarcopenia. It is preferable, where possible, to work within a multidisciplinary team including general practitioner diabetologist, geriatrician, dietologist and dietician, physiatrist and physiotherapist.
B. Geriatric DM patients should be categorized as:
   1 Patients with DM and obesity;
   2 Patients with DM and malnutrition;
   3 Patients with DM and comorbid diseases or diabetes complications that may increase the risk of sarcopenia.
C. Recommendations for all three types of patients are to:
   - administer the SARC-F scale (Strength, Assistance, Rise, Climb, Falls) to evaluate the risk of sarcopenia. If the patient screens positive, clinical tests to evaluate muscle strength (e.g., handgrip strength) should be used to identify treatment needs. If possible, body composition and muscle mass should be tested using bioelectrical impedance analysis (BIA) or dual energy X-ray absorptiometry (DEXA). If there is confirmation of sarcopenia, severity (from moderate to severe) and progression should be evaluated;
   - review and monitor nutritional status over time with the aim to modify possible risk factors for malnutrition as soon as possible. In the event of malnutrition (or high risk of malnutrition) a personalized diet plan should be developed. Amino acid supplementation should be considered to improve functioning. In obese patients, personalized diet plans should be developed that aim to achieve appropriate weight loss while maintaining lean body mass, with regular monitoring of weight and comorbidities associated with obesity (e.g., cardiovascular diseases, hypertension, obstructive sleep apnea syndrome). The Mediterranean diet is one of the best nutritional alternatives for most geriatric DM patients. Calcium and vitamin D supplementation is recommended for patients undergoing caloric restriction, to prevent loss of bone mineral density, while physical activity, rather than an increase in protein intake, is important for preserving muscle mass;
   - provide recommendations on physical activity adapted to the patient's comorbidities and physical capabilities.

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2. STRENGTH OF THE RECOMMENDATIONS

The quality of the evidence is moderate. Recommendations are supported by published evidence.

3. SUPPORTING EVIDENCE

See appendix.

4. AREAS OF UNCERTAINTY AND FUTURE PERSPECTIVES

DM patients of all ages are recommended to do 30 minutes/day of resistance training at an individualized level according to tolerance and personal safety. Nutritional interventions in geriatric DM patients must take into account that inappropriate caloric restriction is sometimes associated with protein restriction, leading to a loss in lean mass. Changing protein intake is, therefore, essential for maintaining and increasing muscle mass. Protein intake of 1.0-1.2 g/kg/protein is recommended, which must be adapted according to the patient's comorbidities and, if necessary (e.g., during an acute event) increased up to 1.5 g/kg/day.
The role of dietary interventions in geriatric DM patients deserves further exploration. Several studies have shown that timing and quality of protein intake are important, also depending on the type of physical activity carried out, and that amino acid supplementation may improve muscle performance. Leucine is the amino acid that has been shown to have the best anabolic action, which triggers the Rapamycin pathway. Dietary supplementation with creatine in combination with physical exercise can lead to an increase in muscle mass, strength, and resistance compared to physical exercise alone.

APPENDIX

DM is an important risk factor for the development of physical disability in older patients [1].
Sarcopenia is defined as age-related loss in muscle mass and function. Sarcopenia is a complex syndrome, characterized by loss of muscle mass, in isolation or associated with an increase in fat mass. Causes are multi-factorial and include chronic degenerative diseases, age-related changes to the endocrinological system, chronic inflammation, insulin resistance, lack of mobility, and nutritional deficiencies [2]. According to the European Working Group on Sarcopenia in Older People 2 (EWGSOP2) the first parameter that should be assessed during sarcopenia diagnosis is muscle strength, defined as low muscle quality and quantity [3]. A wide variety of clinical and instrumental tests are available for assessing sarcopenia [4] but the recommended assessment scale is SARC-F, which consists of five questions used to stratify the risk of sarcopenia in older persons [5], and is a valid tool for assessing patients with T2DM [6,7].
Sarcopenia is one of the main factors for developing the frailty phenotype proposed by Fried et al. [8]. An individual who develops at least three out of the five clinical components proposed by Fried (weight loss, weakness, exhaustion, slowness, low physical activity level) is defined as frail [8]. Sarcopenia occurs as an intermediate stage during the development of frailty. The prevention and early detection of sarcopenia is a key aspect of the clinical management of geriatric DM patients [9].
EWGSOP2 has developed several methods for the early identification of sarcopenia. In clinical practice, the most validated, reliable and cost-effective technique for identifying patients at risk of sarcopenia is the Gait Speed Measurement [10]; with a cut-off speed of < 0.8 m/s used to define risk of developing sarcopenia. Once a patient has been identified as at-risk, they should be referred for a diagnostic evaluation of muscle mass with Dual Energy-X-ray absorption (DEXA) estimating the appendicular skeletal muscle mass (ASM) index (ASM/height2) and using a cut-off of 7.26 kg/m^2 in men and 5.5 kg/m^2 in women. A valid alternative is the estimation of ASMI using Bioelectrical Impedance Analysis (BIA), with a cut-off of 8.5 kg/m^2 in men over 65 and 5.75 kg/m^2 in women over 65 [11].
Muscle mass measurement should then be completed by assessing muscle strength. Handgrip strength correlates with both lower limb muscle capacity and Activities of Daily Living [12] and, thus, is a useful clinical marker that can be used to screen for sarcopenia in geriatric patients, defined as Handgrip Score < 30 kg in men and < 20 kg in women [12]. In the future, handgrip monitoring could be used to assess the effectiveness of therapeutic interventions aimed at slowing down sarcopenia.
The Short Physical Performance Battery (SPPB) is a composite scale used to measure physical performance which can be used to detect sarcopenic early in geriatric persons [13]. It assesses balance, gait, and endurance by assessing the patient's ability to perform various maneuvers, including standing with feet together, walking in tandem, and standing up from a seated position on a chair five times. This last exercise, the Chair Stand Test, can be a reliable index on its own. Scores range from 0 to 12, with less than 6 indicating poor performance.
Frailty is associated with an increased incidence of adverse events such as disability, hospitalization,

increased risk of falls, and all-cause mortality [14]. As sarcopenia is an intermediate stage that occurs during frailty development, the two syndromes overlap. Thus, it is useful for identifying frail patients as early as possible through rapid screening tests such as the 'FRAIL' Questionnaire Screening Tool, which defines frailty as the presence of > 3 frailty symptoms or, alternatively, the Cardiovascular Health Study Frailty Screening Scale (CSF) [15].

It is noteworthy that there are many risk factors for sarcopenia in older diabetic patients and they often have a synergistic effect, suggesting a cause-effect relationship between sarcopenia and DM [16]:

- Increasing levels of inflammatory cytokines such as TNF-a and IL-6 have a detrimental effect on muscle mass and function [17]. There is a high correlation between IL-6 serum levels of and muscle mass [17]. In addition, a decline in IGF-1 levels has an antiproteolytic effect [18].
- Insulin-resistance, on the other hand, causes muscle atrophy by inhibiting the Rapamycin pathway, which is implicated in muscle protein synthesis [19]. Reducing testosterone levels in DM patients reduces muscle protein synthesis [20].
- DM increases Angiotensin II levels [21], which are responsible for the cleavage of actin from myosin, which leads to muscular atrophy through proteolysis via the ubiquitin/proteasome pathway. The use of ACE-inhibitors has been associated with an increase in muscle strength [22].
- Muscle atrophy also increases in the presence of diabetic neuropathy: the degradation of the neuromuscular junction is a predisposing factor for muscle atrophy and loss of muscle strength [23].

Obesity in DM patients also compounds the situation, due to an often-misunderstood syndrome of sarcopenic obesity, which is characterized by a reduction in lean muscle mass without a decrease in excess adipose tissue mass [24]. The incidence and prevalence of sarcopenic obesity increases with age and is associated with a higher mortality risk in older patients [24,25]. However, sarcopenia linked to malnutrition, which often results from poor protein-caloric intake, inability to eat, and any chronic disease that affects proper nutrition, should not be underestimated in geriatric patients [3].

Changes to the mouth, which occur in geriatric patients and are often more pronounced in DM patients, such as edentulism, parodontitis, xerostomia, and dysgeusia, can play a central role in the progressive decrease in protein-caloric intake due to worsening chewing and swallowing. This leads to patients choosing to eat mostly soft or creamy foods that are often inadequate for sufficient protein intake unless they are carefully balanced [26,27]. Together with these mouth changes, studies also reveal that cognitive decline plays a role, leading to problems in swallowing, dysphagia, and food choice, which can worsen malnutrition, leading to sarcopenia [26-28]. Therefore, a nutrition assessment is recommended during the evaluation and management of geriatric DM patients, which can be carried out with various screening tests (Malnutrition Universal Screening Tool -MUST; Mini Nutritional Assessment-MNA; Malnutrition Screening Tool -MST) that can identify patients at high risk of malnutrition [29,30].

Numerous drugs are currently available for the treatment of T2DM, but treatment of geriatric DM patients must take into account the risk of sarcopenia associated with this disease. Insulin therapy plays a role in preventing skeletal muscle atrophy by increasing protein synthesis and decreasing degradation, although its protective role has not yet been fully established in geriatrics patients [16,31-33]. Insulin sensitizers have been shown to reduce lean body mass loss by slowing down the process of sarcopenia in geriatric patients. SGLT-2 inhibitors, which have an indirect action on insulin sensitivity, could have a positive effect on sarcopenic patients, even though this has not yet been confirmed in clinical trials [31-34]. The role of metformin is still controversial: numerous studies suggest a catabolic effect through skeletal muscle autophagy [31,34] while recent cancer models demonstrate a protective role of this drug in the process of muscle mass loss [34,35].

Due to their mechanism of action, it was initially thought that glitazones could be promising agents for preventing sarcopenia, but their clinical use and efficacy are controversial because they have an unfavorable risk-benefit profile (e.g., increased adverse cardiovascular events) [36]. Some sulfonylureas can cause muscle atrophy associated with loss of muscle protein by reducing fiber size [34].

Non-pharmacological interventions such as physical activity and personalized diet plans should also be considered for managing DM patients, to improve glucose metabolic compensation and insulin sensitivity [37]. These strategies can have a significant impact on improving body composition by reducing weight and increasing lean mass. Resistance training is the most effective strategy for increasing the muscle mass and function in persons with sarcopenia and for improving the metabolic health of T2DM diabetes. The effect of resistance training on sarcopenia in geriatric DM diabetes patients has not be adequately studied and in clinical practice this intervention may be hindered by chronic diseases that limit mobility [38].

DM patients of all ages are recommended to do 30 minutes/day of resistance training at an individualized level according to tolerance and personal safety [4,37-39]. Nutritional interventions in geriatric DM patients must

take into account that inappropriate caloric restriction is sometimes associated with protein restriction, leading to a loss in lean mass. Changing protein intake is, therefore, essential for maintaining and increasing muscle mass. Protein intake of 1.0-1.2 g/kg/day is recommended, which must be adapted according to the patient's comorbidities and, if necessary, increased up to 1.5 g/kg/day, for example in case of an acute event [39-41]. Recent studies in geriatric patients without diabetic nephropathy have shown that a daily protein intake of 30% of total caloric intake can improve glucose metabolism and, them the need of antidiabetic drugs.

The role of dietary interventions in geriatric DM patients is still unexplored [39]. Several studies have shown that timing and quality of protein intake are important, depending on the type of physical activity carried out, and possible amino acid supplementation that could improve muscle performance. The amino acid that has the best anabolic action is Leucine, which triggers the Rapamycin pathway [42]. A randomized trial in a population of sarcopenic geriatric patients demonstrated that a daily intake of at least 8 g of essential amino acids, including Leucine, led to an increase in muscle mass and insulin-sensitivity with a reduction in TNF-a levels [43].

A randomized, double-blind trial in a population of men over 70 years old, demonstrated that dietary supplementation with Creatine, in combination with physical exercise, led to an increase in muscle mass, strength, and resistance compared to physical exercise alone [44].

Ethical consideration

None.

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Conflict of interest

The Author declares no conflict of interest.

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This statement is:	**Quality of the evidence** (in the case of recommendation):
☒ **Recommendation** (supported by published evidence) ☐ Best practice (supported by expert opinion)	☐ Low ☒ **Moderate** ☐ High