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CARLA TASK FORCE ON SARCOPENIA: PROPOSITIONS FOR CLINICAL TRIALS*

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Abstract: In the presence of an aging population, public health priorities need to evolve. As the populations gets older, the already existing pathologies have become commonplace with specific geriatric clinical syndromes like frailty, mobility disability, or cognitive impairment, among others. Sarcopenia is a good example for which geriatricians, neurologists, physiologists, nutritionists and epidemiologists need to find a consensual definition and diagnostic tool as well as guidelines for the management of clinical trials and possible treatments. The Carla Sarcopenia Task Force, which met in the south of France (Toulouse) for an expert consensus meeting called "Les Entretiens du Carla", have addressed a series of existing issues to place Sarcopenia into a nosological context: a definition which should be a composite of a change in muscle mass and a change in strength/function depending on either a progressive and chronic wasting process or an acute onset of loss of muscle mass; a recommendation for DXA and the Short Physical Performance Battery as a clinical pragmatic approach of Sarcopenia; a differentiated approach for clinical studies according to prevention or treatment objectives and depending on the sub-groups and target populations; and finally, a summary of therapeutic strategies currently recommended. The aim of "Les Entretiens du Carla", based on an expert meeting panel, was to address a series of unsolved issues in the field of Sarcopenia by combining the expert opinion with a revision of the existing literature on the topic. Through this report, the reader will appreciate the determination to find conclusions on the various issues and further studies to be developed to determine the best multidisciplinary approach needed.

Definition for Sarcopenia ?

Analysis of previous definitions

The early definition of Sarcopenia proposed by Rosenberg (1) (age-related loss of mass) is questioned.

1. The various tools used to define "loss of mass" have in fact lead to defining the cuts-off for "low muscle mass" in a healthy population. Indeed, the definition considered values below 2 standard deviations (SD) under the mean of a reference population (younger than 40 years old) as sarcopenic. As people age there are more individuals under the cut-offs because it is known that muscle mass naturally decreases with age. In fact, it needs to be considered that sarcopenia (loss of mass and function) is a dynamic process and whichever operational definition is chosen, it should sense a rate of change, ideally related to geriatric health outcomes.
2. Based on the different definitions of "low muscle mass" (mass divided by weight, mass divided by height, or mass assessed by CT scanning imaging), the prevalence of sarcopenia varies widely between cohorts and it is conceivable that the prevalence varies by genders.
3. Various tools have been used (Dual Energy X-ray Absorptiometry, DXA, Bioelectrical Impedance Analysis, BIA, or CT scanning) leading to various prevalence rates. DXA measures fat mass, bone mass and indirectly the mass of non fat, non bone tissue in the limbs, being the best available index of appendicular muscle mass. BIA makes assumptions about the electrical conductivity across the body (which may change with the change in muscle mass and quality) and derives muscle mass from resistance opposed by the whole body to an electrical current.
4. Fat mass has been shown to contribute significantly to functional impairment in elderly people independently of muscle mass. The definition proposed for sarcopenia during the meeting of the Carla Sarcopenia Task Force accounted for the assessment of muscle mass and function, and fat mass. It was stated that after adjustment for covariables people with residuals below the 20th percentile were considered sarcopenic. With such a definition, sarcopenia predicted functional impairment in a more sensitive way.
Sarcopenic obesity was associated with increased mobility disability compared to sarcopenia without obesity. This may indicate that the combination of high fat mass and low

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muscle mass is detrimental and highly predictive of functional decline.

5. Muscle strength is related to both muscle mass and adverse health outcomes in older people (like falls, onset of persistent disability, hospitalisations or increased risk of mortality). In many of the earlier studies the relationship between adverse outcomes and muscle mass did not take strength into consideration. When the adjustment for muscle strength was performed, these outcomes were better predicted and muscle mass was no longer a significant predictor. Dynapenia (defined as the loss of strength) appears therefore as a useful indicator as part of the definition of sarcopenia.
6. Risk factors for loss of muscle are identified. They include hormonal status, protein metabolism, energy metabolism, neuronal function and reduced physical activity.

Proposition 1: Definition proposed by the panel of experts

The definition of sarcopenia should be close to the initial Rosenberg definition.

1.1. Definition should be a composite of a change in mass and a change in strength/function. It is hoped that the definition is valid in both the ageing population and individuals enrolled in clinical studies so that the indicators are the same for epidemiological studies and clinical trials.

1.2. The chosen criteria should be associated with/or predict future relevant geriatric adverse outcomes (disability, falls, mobility, hospitalisation institutionalisation, or increased mortality) according to thresholds based on expert consensus. The constraints are listed in the table 1.

Table1

Clinical measures of sarcopenia

• Valid	• Non-invasive
• Reliable	• Practical
• Specific for muscle	• Low cost
• Sensitive to change over time and with interventions	• Widely accessible
• Predict geriatric outcomes	• Results consistent across large cohorts in diverse populations

1.3. If a "low muscle mass" criterion is chosen rather than a change with time, it should be proven that a one time assessment is a valid predictor of functional decline and the risk of suffering adverse outcomes.

1.4. It appears very important to include an assessment of fat mass, so that the mass component of the definition is a composite of changes in muscle and fat mass. The threshold for the low muscle and high fat mass criteria is not known. More research is needed to identify these thresholds

1.5. DXA appears as the technique to be used because of its precision, and because it measures muscle and fat mass at the same time. More research is needed to assess the relative contribution of muscle and fat mass to functional decline and their change over time (in mass per body weight, mass per m^2, or as residuals). If residuals are used they should be user friendly for clinicians, based on easy to perform computations.

1.6. The functional component of muscle mass will probably be related to muscle strength. Grip strength is attractive because it is simple. More work is needed to assess its validity in all situations (ageing and clinical fields). Gait speed could be an alternative although it is not specific of muscle strength. The use of physical performance indicators of function may not be muscle specific. Since these aspects (strength and muscle function) have been considered more as consequence than as a part of the definition, other tools to assess strength may prove useful.

Recommendation for Clinical evaluation of Sarcopenia

Different techniques have been mentioned, which are potentially interesting for research, but not possible in many clinical sites.

The issue of physical performance has been discussed and the short performance battery (SPPB) was mentioned with emphasis. The SPPB is a well validated tool and was shown to be responsive to intervention and associated with a clinical meaningful change.

Minimal clinical relevance is established to one point, it's a data-driven anchor, which is extremely important In most of the fields, we don't have data-driven anchors for the minimal clinical relevance.

Measurements

• Muscle size:
  – Gold standard: MRI
  – Good compromise: DXA
  – There other less characterized measures.
• Physical performance
  – SPPB: validated, responsive to chance, MCRD established experimentally 1 p.
  – 400 m walk
• Biomarkers: no specific; research value

Proposition 2: DEXA for a clinical pragmatic approach

For assessing muscle size, the gold standard for the moment is Magnetic Resonance Imaging (MRI), but it is an expensive technology. So maybe the good compromise is performing DXA for a clinical pragmatic approach.

Which clinical trials should be performed?

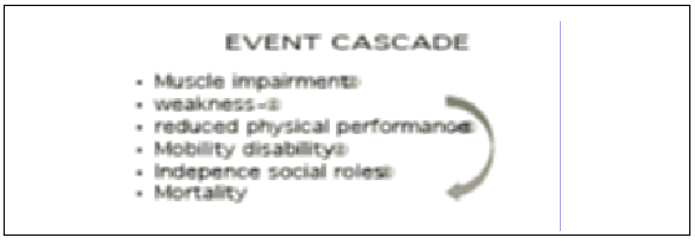
To convince regulators, we need to show the existing data in a "very strong way". It is important to emphasize that there is a relationship between weakness and mortality, which is very interesting since weakness can be an early step of the model and is easy to measure.

Proposition 3: To clarify goals of clinical trials: prevention or treatment

We should clearly distinguish prevention from treatment trial designs (primary versus secondary prevention).

3.1. Prevention aims to reduce a future adverse health event, which may occur sooner or later depending of the risk set of a person. Sarcopenia may be an important risk set enhancing the chance of future weakness and functional decline. Thus, we could select sarcopenic individuals and perform a prevention trial:

- To prevent weakness
- To prevent reduced physical performance
- To prevent mobility disability



3.2. Treatment aims to ameliorate or revert a given stage in the cascade of events

The very first recommendation is to say that the field (sarcopenia) is really not mature to make recommendations for confirmatory trials.

The field of sarcopenia is not mature because it needs official recommendations related to the definition of the disease (the syndrome), the target population and the definition of subgroups.

This is the place where work must be done, and this has to be resolved before confirmatory trials are being planned.

Proposition 4: A randomized control trial

The outcome measures are much better characterized than in other fields: it's very rare to have data-driven minimal clinical relevance differences, or to have clear correlations between early measures, to late outcomes.

4.1. We cannot have any other kind of design than a randomized control trial

It should be a parallel group design; crossover trials may not be ideal in this setting.

4.2. The comparator will be the best standard of care

We need to take the opportunity of any trial that has been done in this field to try to understand the pattern of the placebo effect or at least the pattern of the best standard of care, so this will be extremely important to plan the so called confirmatory trials in a later phase.

4.3. Follow up

If we believe that a program of physical activity is part of the best standard of care, most likely any trial will have to be done on top of some exercise program which is a challenge for any intervention targeting muscle mass/strength. Then just as a benchmark numbers, recommendations of follow up are:

- Planning a prevention trial (with the definition in recommendation 3.1), recommendations are to have a 2 to 3 years at least of follow-up (depending on the outcome, falls may need a shorter follow-up).
- Planning a treatment trial, it has to be 3 to 6 months at least.

4.4. Target group

Defining the study population is an important first step; most certainly one would want to target participants with the "risk" profile of interest – sarcopenia -; this will increase the event rate of important endpoints and thereby optimize power to detect a meaningful difference between the intervention and the control group. We have to make an effort on what is the definition of sarcopenia, that this definition can be reliable and applicable across centres and across investigators.

Then of course we have to consider again the goal of the trial. The main dichotomy is prevention versus treatment trials:

- If we are speaking of prevention, we might include patients who are good compensators, because prevention is something that happens in a total, the patient with all his comorbidities and all his problems while,
- If we are speaking of treatment, we need to be much more selective in finding a target population with an important muscle impairment.

And finally, we need a good definition of the known comorbidities, so that we obtain a clear baseline of non-confounders. Nutritional status, a nutritional frequency questionnaire, and information on the presence of nutritional supplements and co-medications should also be obtained. If there are any plausible genetic markers, they should be assessed. In the absence of these markers, biobanking should be planned in case of future scientific progress.

Proposition 5: Outcomes measures

5.1. Main outcomes measures

- DXA to assess muscle mass, and eventually fat mass and bone mass
- Muscle strength
- SPPB, as the preferred assessment tool by regulatory agencies. For exploratory trials and for treatment trials, a measure of physical performance (like the SPPB) should be the primary outcome.

For exploratory trials and for treatment trials, the measure of physical performance (SPPB) should be the primary outcome.

Patients particularly disabled

Some outcomes measures cannot be applicable to all individuals: if individuals are in the stage they are so disabled that they cannot perform these outcomes, it's not a regular sub-grouping because you cannot put in a trial patients that cannot perform on the outcomes of this trial; so it will be immediately an exclusion criteria. This brings us to the development of scales or outcomes for this special group of patients that are particularly disabled.

5.2. Others outcomes

- There is a need to establish a level of disability, with an agreed score.
- Concerning biomarkers, any combination of interest can be justified if we have only exploratory value. So it's possible to combine or use all of them, it is a matter of cost, and practical logistical considerations.
- Time spent in care by the care-giver is an important secondary, not primary, outcome in an exploratory (prevention) trial.
- Time-to-event is the best choice for secondary outcomes in prevention trial. These trials are usually evaluated with large groups of secondary outcomes; in this particular population, we have to balance quite well what to put in the list of outcomes to avoid overburdening.

5.3. Discussion on the future of confirmatory trials

- It is accepted that there is a good relationship between physical performance and later outcomes like disability onset or mortality. By changing physical performance, you can change the risk of disability onset. Although the existing data prove casual relationship, replications of these results are needed. If this is not the case, regulators will not accept for confirmatory trials just a physical performance measure as a main outcome.
- Gait speed is also an interesting outcome measure that should be discussed.
- Missing data. The best way to deal with real missing data is to have the retrieval of the dropouts which is not easy of course. For imputation of missing data nowadays it is recommended in Europe to use multiple imputation strategy and to use ICF as a sensitivity analysis.

Validated treatments and therapeutic perspectives

Considerable evidence suggests that sarcopenia is a reversible cause of disability and could benefit from intervention, especially at its early stages. However, the effects and ability of these interventions to improve function and prevent disability and reduce the age-related skeletal muscle decline in elderly are unknown with existing contradictory epidemiological data (2-4).

2 types of sarcopenia are suggested to exist in older people

1. A primary form of sarcopenia understood as a progressive and chronic wasting process affecting most older people, inducing mobility disabilities at different rates (probably due to exogenous environmental factors like comorbidities and endogenous factors like gene expression).
2. A secondary form of sarcopenia understood as an acute onset of loss of muscle mass in relationship to acute events (like bed-rest, acute catabolic processes, or hormone deficiencies, for instance) that accelerates the rate of muscle loss and accelerates the onset of mobility disability

Proposition 6: 2 types of sarcopenia

Two types of sarcopenia are suggested to exist:

- a primary form of sarcopenia understood as a progressive and chronic wasting process,
- a secondary form of sarcopenia understood as an acute onset of loss of muscle mass.

Obviously the treatment of the 2 wasting processes is different.

To prevent primary sarcopenia, measures like resistance training, lifestyle modifications and possible long-term (and proven) medications could be implemented.

In secondary sarcopenia, the identification of possible causes contributing to the process is crucial and intervention may be best developed in the context of these modifiable causes.

Proposition 7: Physical activity

7.1. No pharmacological or behavioural intervention to reverse sarcopenia has proven to be as efficacious as resistance training.

The American College of Sport Medicine and the American Heart Association suggested that training produced gains in muscle size and strength, even in frail elderly (5, 6). Resistance training in elderly increases muscle size (between 5 and 10%) with a modest increase in strength. Most of this increase in strength is due to neural adaptation of the motor unit pathway and disuse results in a rapid detraining (7, 8).

7.2. Several reports suggested that maintaining the benefits from resistance training is possible with as little as one exercise program per week (9), but organizing resistance training sessions and programs are challenging in frail elderly subjects and some practitioners are reluctant to prescribe high intensity exercise in elderly patients.

7.3. Currently, only 12% of the United-States elderly population performs strength training at least twice a week (10).

Proposition 8: Nutrition

In older people, beyond their constitution, the presence of weight loss resulted in loss of muscle mass and increased rate of mortality (11). Weight loss and calorie restriction should be avoided after the seventh decade of life (12, 13) especially if it results in a reduction of BMI scores with no reduction in waist circumference. While waist circumference is related to the presence and risk of cardiovascular diseases, and its reduction could diminish the risk, BMI is related to total body mass and lean mass.

In malnourished older people, poor protein intake limited the efficacy of interventions such as resistance training in terms of muscle tissue and strength gain. Increasing protein intake in older people and especially in frail elderly (higher than the recommended 0.8g/kg body weight per day) could minimize the muscle-wasting process (14). Higher protein intake was associated with a significant increase in lean mass in older people (15), but it is not clear if protein supplementation in the absence of malnutrition enhances muscle mass and muscle strength, as protein supplementation alone or in association with physical training has proved unsuccessful (16).

New approaches, based on specific nutriments, including essential amino acids (namely Leucine) have suggested anabolic effects (17, 18). It has been recently reported that essential amino acids stimulate protein anabolism in older people whereas non-essential amino acids add no supplementary effect when given in association (19, 20). The acute muscle protein synthesis in response to resistance training and essential amino acids ingestion is similar in old and young subjects but delayed in older subjects (20).

8.1. Quantity and quality of amino acids

The quantity and quality of amino acids in the diet are important factors for stimulating protein synthesis, and nutritional supplementation with whey proteins, a rich source of Leucine, could be a strategy to prevent sarcopenia (21, 22).

8.2. Schedule of the protein supplementation

Even more, the schedule of the protein supplementation was relevant to improve muscle protein synthesis, and a large amount of amino acid supplementation in one meal per day seemed to be more efficient in increasing the anabolic effect than intermittent protein intake (23). Thus, the anabolic effect of protein supplementation may be maximized with a large amount of a highly efficient nutritional supplement (such as essential amino acid and especially Leucine) once a day.

Protein supplementation

In association with strength training, the timing of the protein supplementation may also affect muscle tissue anabolism. Protein supplementation taken immediately after resistance training produces a 25% increase in quadriceps muscle cross-sectional area, compared to the supplementation taken between the training sessions. Finally, no increase has been noticed if the supplementation was given at a distance from the training session (24). The prevention of sarcopenia should occur throughout life and the possible influence of specifics exposures at critical development periods may have a major impact on the risk of sarcopenia in old age (25, 26).

8.3. Diet

A well balanced diet, along with adequate amounts of essential minerals, fatty acids and amino acids, together with an active and healthy lifestyle with regular periods of aerobic and resistance training would be a correct life-course approach toward reducing the prevalence of sarcopenia and other chronic diseases in future elderly generations.

Proposition 9: Pharmacological treatments

9.1. Testosterone

Testosterone is currently not recommended for the treatment of sarcopenia, and the associated side-effects limit their use.

The potential risks associated with testosterone therapy (e.g. increased of prostate-specific antigen, hematocrit and cardiovascular risks) compared to the low level of evidence concerning the benefits on physical performances and function explain the actual recommendations (29) and high doses of testosterone have not be given in RCT for the fear of prostate cancer (30), with existing data, from the Baltimore Longitudinal Study on Aging, reporting a positive correlation between free testosterone blood level and prostate cancer (31).

New synthetic androgen modulators such as the 7 -methyl-19-nortesterone (or MENT or trestolone) are a potential alternative to testosterone, but randomized trials have not been conducted. MENT has an anabolic effect on bone and muscle in rats and may have small negative effects on prostate. Another therapeutic perspective is the Selective Androgen Receptor Modulators (SARMs) that has the same anabolic effect on muscle tissue as testosterone without the known side-effects. These new drugs may expand the clinical application of androgens in sarcopenia as they enter the clinical phase of research.

Testosterone - Updating Data

About 20% of men older than 60 years and 50% of men older than 80 years are considered hypogonadic defined as a total testosterone concentration of 2 standard deviations (SD) below the mean of healthy young men (27). There are conflicting and inconclusive results of the effectiveness of testosterone therapy on muscle mass and muscle strength in older people. Some interventional studies report a modest increase in lean mass and most report no increase in strength (16). The scarce studies that have reported an increase in strength, the magnitude observed was lower than the increase obtained by resistance training. Moreover, the anabolic effect of testosterone on lean mass and strength seems weaker in older people than in young (16). A recent meta-analysis indicated that there is a moderate increase in muscle strength among men participating in 11 randomized studies (with one study influencing the mean effect size) (28).

9.2. Growth hormone

GH increases muscle strength and mass in young subjects with hypopituitarism, but in older people, who are frequently GH-deficient, most of studies report no increase in muscle mass or strength even if associated with resistance training (16, 32).

Even more, it has been described that GH increases mortality in ill malnourished persons (33), and many studies highlight potentially serious and frequent side-effects such as arthralgia, oedema, cardiovascular side-effect and insulin resistance (34).

To date, there is little clinical research to support the use of GH supplementation to treat sarcopenia. Experimental studies have shown that GH is able to induce IGF-I mRNA production and increase suppression of cytokine signaling-2 (a cytokine-inducible protein that inhibits cytokines production through a negative feedback mechanism) in myoblast cell (35).

Previous observations examining the association of IGF-I with muscle strength and physical performance in older people provide conflicting results (36-38). Interestingly, in a study among obese postmenopausal women, the administration of GH alone or in combination with IGF-I caused a greater increase in fat-free mass and a greater reduction in fat mass than those achieved by diet and exercise alone (39). However, the clinical applications of these findings are limited by safety issues as recent studies have found that IGF-I correlates with increased risk of prostate cancer in men, pre-menopausal breast cancer in women, and lung cancer and colorectal cancer in both men and women (40).

9.3 Myostatin

Antagonists of myostatin drug (such as follistatin or caveolin-3) have a potential therapeutic impact in future studies on sarcopenia.

Myostatin is a recently discovered natural inhibitor of muscle growth (41), and mutations in the myostatin gene result in muscle hypertrophy in animals and in humans (42, 43). Antagonism of myostatin enhanced muscle tissue regeneration in aged mice (43) by increasing satellite cell proliferation.

Recombinant human antibodies to myostatin (myo-029) are actually tested in RCT in muscular dystrophy, and a soluble activin type IIB receptor that reduces myostatin effects is actually in development. A single gene myostatin inhibitor enhances muscle mass and strength in mouse. All these new approaches may be relevant to the treatment of sarcopenia in the future.

9.4. Estrogens and Tibolone

A recent review on the effect of estrogen and tibolone on muscle strength and body composition (44) reported increased muscle strength but only tibolone appeared to increase lean body mass and decrease total fat mass.

Tibolone is a synthetic steroid with estrogenic, androgenic and progestogenic activity. HRT and tibolone may both react with the intra-nuclear receptor in muscle fibres (45, 46), and tibolone may also act by binding androgen receptors in muscle fibres and increase free testosterone and GH. However, further research is needed to confirm these findings and the long-term safety of these drugs in elderly population. In fact, no study has currently confirmed the positive findings in older persons.

9.5. Vitamin D

The effects of vitamin D on fractures has been summarized in a recent meta-analyses published in 2009 (47). This analysis included 12 published double-blind randomized

controlled trials of oral vitamin D supplementation (n=42,279). The results showed that vitamin D at a dose greater than 400 IU per day reduced the risk of non-vertebral fracture significantly by 20% including all subgroups of the older population, community dwelling (-29%) or institutionalised (-15%), age 65-74 (-33%) or 75+ years of age (-17%), and combined with calcium (-21%) or as a main effect of vitamin D alone (-21%).

Notably, fracture prevention improved significantly with a higher received dose of vitamin D and with a higher achieved 25-hydroxyvitamin D level, both for any non-vertebral fractures and for fracture of the hip. This benefit may in part be explained by a direct benefit of vitamin D on muscle resulting in less falls and thereby contributing to less fractures.

This is supported by the presence of the VDR in human muscle tissue (48) and a rapid (49, 50) and sustained (51-54) effect of vitamin D on falls from several trials. A most up to date meta-analysis (in press at BMJ) summarizes 8 double-blind randomized controlled trial with supplemental vitamin D confirming a similar pattern of a dose-dependent benefit on fall prevention with vitamin D (55). Further evidence on a direct effect of vitamin D on muscle is derived from several double-blind randomized controlled trials in frail and community-dwelling older individuals showing a significant improvement in strength and function with treatment (50, 53, 56).

9.6. Creatine

Creatine supplementation is supposed to increase muscle mass synthesis (57) by increasing intra muscular creatine and phosphocreatine, which allows increased resistance training to stimulate muscle mass synthesis.

Several mechanisms for this action are hypothesized such as an increased expression of myogenic transcription factors, but the few clinical trials in older people (in addition to physical training or not) reported conflicting results (58-63). With the actual data It is unknown if creatine supplementation can prevent or reduce sarcopenia, disability or morbidity (50, 64).

9.7. Angiotensin II Converting Enzyme inhibitors (ACE inhibitors)

Growing evidence suggests that ACE inhibitors may prevent sarcopenia (14, 65, 66).

The activation of the renine-angiotensin-aldostrone system may be involved in the progress of sarcopenia. Angiotensin II infused in rats results in muscle atrophy, and several mechanisms such as influences on oxidative stress, metabolic and inflammation pathway have been suggested through epidemiological and experimental studies.

ACE inhibitor reduces the level of angiotensine II in vascular muscle cell, decreasing the inflammatory markers (via ACE inhibitors), improving microvascular endothelium and blood flow, and consequently slowing muscle loss (67, 68).

ACE inhibitors may also improve exercise tolerance via changes in skeletal muscle myosin heavy chain composition (69). The ACE gene polymorphism also affects the muscle anabolic response and muscular efficiency after physical training (70).

9.8. Cytokine inhibitors

The age-related inflammation process is supposed to be an important factor in the development of sarcopenia, and anti-inflammatory drugs may delay its onset and progression. Cytokine inhibitors, such as thalidomide, increase weight and lean tissue anabolism in AIDS patients (71).

TNF produces muscle tissue atrophy in vitro. Anti-TNF antibodies, a treatment provided to rheumatoid arthritis patients, may also be an alternative therapeutic opportunity for sarcopenia (72). However, the benefit/risk balance of these drugs is a major limitation that has not yet been tested in sarcopenic patients. Epidemiological data also suggest that fatty fish consumption rich in the anti inflammatory actions of omega-3 fatty acid may prevent sarcopenia (73).

Proposition 10: Genes

Many genetic factors contribute to muscle mass and strength and treatments based on the physiopathology of sarcopenia can be expected in the future. Understanding the fundamental pathways leading to sarcopenia, such as the expression pattern of genes and proteomics will probably determine future treatment strategies (74, 75).

Proposition 11: Apoptosis

Although evidence of the role of apoptosis on sarcopenia is lacking in human studies, recent experimental studies suggest that apoptosis may be a determinant factor leading to muscle loss.

Our understanding of the mechanisms of apoptosis suggests that caspase inhibitors may represent a possible future therapy (76).

For instance, exercise training reverses skeletal muscle apoptosis (77) and caloric restriction reduces apoptosis pathways stimulated by TNF (78). Redox modulators such as carotenoids seem to be important factors in influencing loss of muscle strength, functional limitation and disability. Interest in all these molecules is actually suggested by basic research but must be studied in future clinical trials. The Sarcopenia Task Force has underligned the recent knowledged on epidemiology (79, 80), physiopatology (81, 82), target population (83), outcome (84), are important for therapeutic perspectives including nutrition (85), physical activity (86) and new treatment (87).

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