REVIEW

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Wackerhage H[1]

Sarcopenia: Causes and Treatments

Sarkopenie: Ursachen und Behandlung

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Summary

- **Low birth rates** and increased life expectancies have led to population aging e.g. in Japan and Europe. Aging is a time-dependent functional decline that affects most living organisms.
- **The loss of muscle mass** and function during normal aging is termed sarcopenia. Sarcopenia is due to many factors including a loss of motor neurons and muscle fibers, type II fiber atrophy anabolic resistance (i.e. less muscle protein synthesis after protein ingestion, resistance exercise and insulin) and impaired muscle regeneration.
- **Sarcopenia** is associated with frailty, mortality, problems with performing daily living tasks and falls.
- **The main treatments** are safe, effective and attractive resistance training programs with up to 40g of protein in the "anabolic window" before, during or after resistance exercise and a daily protein intake of at least 1-1.2g per kg body weight (the amount of protein ingestion is more important than potential timing effects). Additional treatments such as creatine or vitamin D might be useful. Finally, drug treatments such as testosterone, β-agonists or myostatin inhibitors can potentially be used for some subjects with sarcopenia.

KEY WORDS:
Sarcopenia, Satellite Cells, Aging, Anabolic Resistance

Zusammenfassung

- **Niedrige Geburtenraten** und eine längere Lebenserwartung haben das Durchschnittsalter der Bevölkerung, insbesondere in Japan und europäischen Ländern, erhöht. Altern ist der zeitabhängige Rückgang der Körperfunktionen und hat viele Ursachen.
- **Die Reduktion der Muskelmasse** und -funktion beim normalen Altern wird Sarkopenie genannt. Es gibt mehrere Ursachen. Zu den Ursachen zählen, dass Motoneuronen und Muskelfasern beim Altern vermutlich verloren gehen. Zusätzlich atrophieren insbesondere die schnellen Typ-II-Muskelfasern; es entwickelt sich eine anabolische Resistenz (d. h. anabole Reize steigern die Muskelproteinsynthese im alten Muskel weniger als im jungen), und alte Muskeln regenerieren im Durchschnitt schlechter als junge Muskeln.
- **Sarkopenie** geht mit Gebrechlichkeit, erhöhter Mortalität und mehr Stürzen einher. Zudem haben Individuen mit geringer Muskelkraft häufiger Probleme, Aufgaben des alltäglichen Lebens zu bewältigen.
- **Die wichtigste Therapie** ist ein altersgerechtes, sicheres und attraktives, progressives Krafttraining kombiniert mit einer Aufnahme von bis zu 40g Protein idealerweise vor, während oder nach einer Krafttrainingseinheit. Pro Tag werden für Ältere mindestens 1-1,2g Protein pro kg Körpergewicht empfohlen. Ergogene Substanzen wie Kreatin und Vitamin D können die Muskelmasse eventuell weiter erhöhen. Testosteron (Anabolika), β-Agonisten oder Myostatinhemmer sind muskelaufbauende Medikamente, die potentiell in Einzelfällen angewendet werden könnten.

SCHLÜSSELWÖRTER:
Sarkopenie, Satellitenzellen, Altern, anabolische Resistenz

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Introduction

In this review, I will answer six questions in relation to skeletal muscle aging. Why questions? Asking questions is arguably the best framework for research because questions can reduce bias and are more "natural" than hypotheses (21). Also questions such as "Why do we age?", "Why do our muscles age?" and "What can we do about it?" allow us to better connect with those in society that ask these questions. Because of that, this review is framed around six questions on skeletal muscle aging.

Question 1: What Are Global Aging Trends and how Do They Affect Societies?

The world's population is aging on average because fewer babies are born and because people live longer (57). As a consequence, the fraction of older people increases world-wide (57). In 2015, over 20% of the populations in Japan, Germany and Italy were aged 65 years and older (WorldExplorer database). At the same time people aged 15-64 years have decreased (57) so that fewer working young must now support more individuals aged 65 years and older. This demographic shift is a major challenge for all societies affected by it.

Question 2: Why Do We Age?

Aging can be defined as a "time-dependent functional decline that affects most living organisms" (32). Aging has many causes and already in 1990 Medvedev had identified 300 theories of aging (34). The following "hallmarks" of aging have been proposed (32):

1. Deregulated nutrient sensing;
2. Loss of proteostasis (protein homeostasis);
3. Mitochondrial dysfunction;
4. Stem cell exhaustion;
5. Altered intracellular communication;
6. Telomere attrition;
7. Cellular senescence;
8. Genomic instability and
9. Epigenetic alterations.

In summary many mechanisms or hallmarks contribute to aging and the causes and time courses of aging differ from organ to organ and in-between species (26).

Question 3: What Is Sarcopenia?

Skeletal muscle size and function vary greatly at all ages and during normal aging skeletal muscle size and function decline. Skeletal muscle size (25), the number of muscle fibers per muscle (30), the size of muscle fibers (30) and muscle strength (53) already vary at least 2-fold in young individuals. During aging muscles additionally become smaller, weaker and slower (Fig. 1 and 2). For example 75-year-old women and men lose 0.64-0.70% and 0.80-0.98% of their muscle mass and 2.5-3% and 3-4% of their strength per year, respectively (35). This phenomenon is defined as sarcopenia, based on the Greek words sarx for flesh and penia for loss (13, 47).

Some researchers additionally define the age-associated loss of strength as dynapenia (10) but this seems superfluous as broadly defined sarcopenia includes losses of muscle function. An important subtype of sarcopenia is sarcopenic obesity which is defined as the presence of both sarcopenia and obesity (13). A workable diagnosis criterion for sarcopenia is the combination of "low muscle mass" and "low muscle strength" or "low physical performance" (13).

Whilst specific diagnostic criteria for sarcopenia have been published (13) there is still no commonly used, cheap, easy-to-administer diagnostic test to identify patients with sarcopenia.

Question 4: What Causes Sarcopenia?

Many factors contribute to sarcopenia. In the following, five key factors will be discussed:

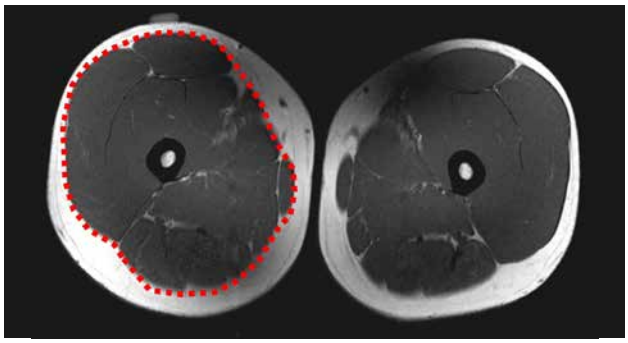

Figure 1

Mid-thigh MRI scan showing a normal, young (18-25 years) male thigh.

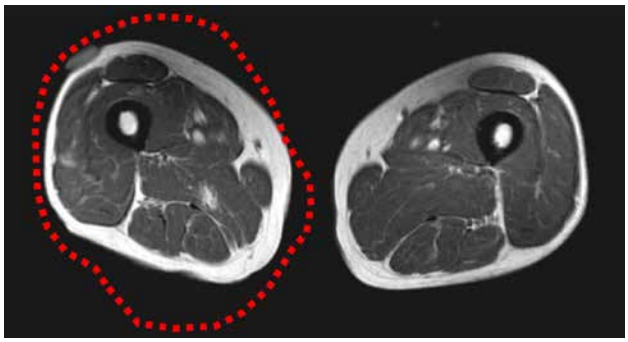

Figure 2

Mid-thigh MRI scan showing a >65 year old male with sarcopenia, in comparison to figure 1. Note the fat infiltration in the sarcopenic individual (45).

1. Loss of motor neurons and muscle fibers and muscle fiber atrophy. Cross-sectional studies suggest that during normal aging, spinal limb motor neurons (56) and up to half of the vastus lateralis muscle fibers (30) are lost. The problem with these studies is, that the individuals were born up to 70 years apart. Because of that, the lower motor neuron and muscle fiber numbers might be due to different environmental conditions and not due to a loss of neurons and fibers during aging. In support of the latter, Nilwik et al (38) did not observe substantially fewer muscle fibers in older individuals (38). However, both Nilwik et al and Lexell et al reported muscle fiber atrophy, especially of type II fibers (30, 38).
2. Anabolic resistance. Muscle fibers hypertrophy if protein synthesis exceeds breakdown. In fasted muscle protein turnover does not differ much between young and old muscle (14). However, when stimulated with essential amino acids (14), resistance exercise (28) or insulin (44), young muscles increase protein synthesis more than old muscles. The reduced response of old muscle to anabolic stimuli has been termed "anabolic resistance". Such anabolic resistance of old muscle, however, is not always observed (7).
3. Impaired regeneration due to reduced stem cell function. Skeletal muscle has an enormous capacity to regenerate after injury. Such regeneration is dependent on satellite cells, the resident stem cells of skeletal muscle (46). When compared to young, old human muscle has fewer satellite cells and regenerates less e.g. after immobilization atrophy (8). This suggests that satellite cells are a key factor in sarcopenia. However, removing almost all satellite cells from young mouse muscles has hardly any effect on skeletal muscle aging (20) which seems surprising. A possible explanation is that satellite cell-depleted muscles of caged mice can age normally. However, in a real life scenario any injury or immobilization ›

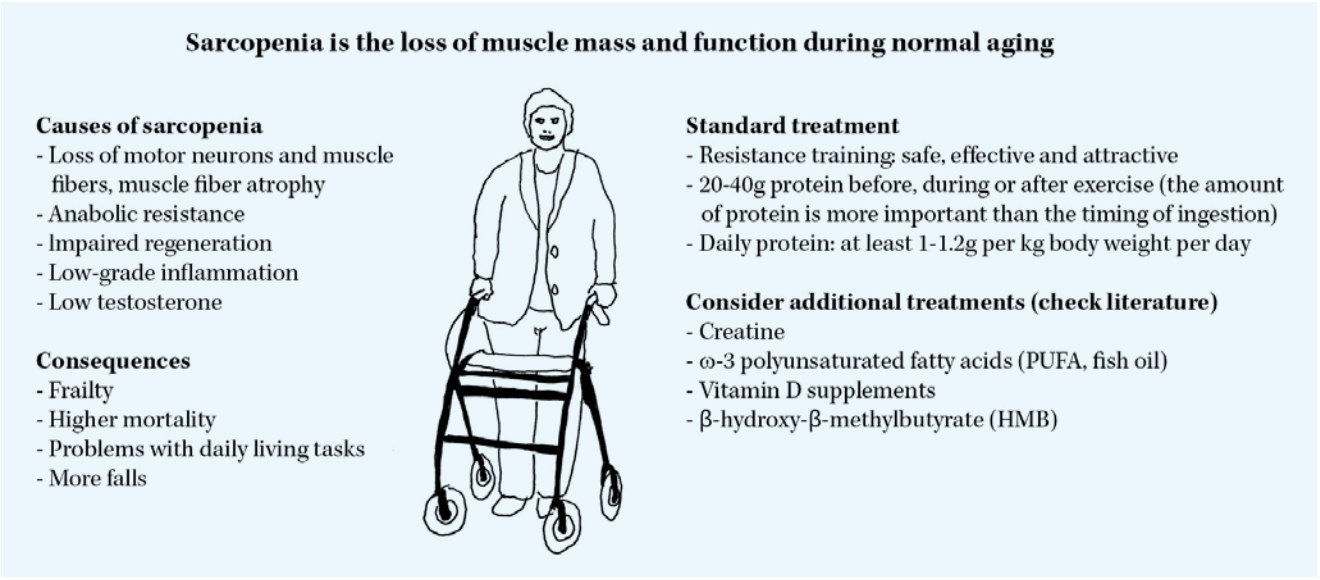

Figure 3
Schematic of the causes, consequences and treatments of sarcopenia.

atrophy will cause a problem because muscles cannot fully regenerate without satellite cells (46). Thus, satellite cells are probably important for the aging of a normally "used" human skeletal muscle.

4. Low-grade inflammation. Aging is associated with chronically increased levels of pro-inflammatory cytokines such as interleukin-6 (IL6) and tumor necrosis factor-α (TNF-α). This is described as chronic low-grade inflammation or as a chronic low-grade inflammatory profile (CLIP) (6). In older men and women, higher levels of pro-inflammatory cytokines are associated with sarcopenia and a greater risk of losing muscle mass and strength (6, 50, 51). Whilst the mechanisms are not fully understood, chronic low-grade inflammation seems to contribute to sarcopenia.
5. Testosterone in hypogonadal men. The concentrations of the male sex hormone testosterone vary at all ages and decline with aging (22, 45). Low testosterone affects muscle mass, because giving between 25 and 600mg of testosterone enanthate to men with suppressed endogenous testosterone increases the cross-sectional area of muscle fibers in a dose-dependent manner (54). Thus, low testosterone concentrations contributes to sarcopenia in hypogonadal males.

In summary, muscle size and function vary greatly at all ages and decline with normal aging, which is termed sarcopenia. Sarcopenia is a slow process caused by many factors including a loss of motor neurons and muscle fibers, anabolic resistance, an impaired regeneration, chronic low-grade inflammation and a decline of testosterone in hypogonadal men.

Question 5: What Are the Consequences of Sarcopenia?

Losing muscle mass and becoming weaker during aging has consequences for health. They are:

1. Frailty: Sarcopenia is associated with frailty (37) which overlaps with sarcopenia but additionally includes weight loss, exhaustion, slow walking speed and low physical activity (19).
2. Mortality: Low strength at middle and older ages is associated with increased all-cause and cancer mortality (3, 12, 48).
3. Daily living tasks: Lower grip strength during middle age is associated with more problems of solving daily life tasks 25 years later (43), suggesting that sarcopenia increases the risk of not being able to live an independent life.
4. Falls: Especially leg weakness is associated with an increased risk of falls (36).

In summary, frailty, high mortality, the inability to carry out daily living tasks and the risk of falling are some of the health issues associated with sarcopenia.

Question 6: How Can We Treat Sarcopenia?

No current intervention will bring back significant numbers of muscle fibers or satellite cells lost during aging. However, progressive resistance (strength) training in combination with nutritional interventions can increase the cross-sectional area and function of muscle fibers. Key anti-sarcopenia interventions are:

1. Progressive resistance (strength) training. Resistance training increases muscle protein synthesis (28), the size especially of type II fibers (27, 38), muscle size and strength in old men and women (15, 31, 40). The increase of muscle protein synthesis after resistance exercise depends on the mechanistic target of rapamycin (mTOR), as blocking mTOR with rapamycin prevents the increase of muscle protein synthesis after resistance exercise (17). Even over 90-year-old individuals can increase their muscle function through resistance training (27). This identifies progressive resistance training as an effective intervention to improve muscle strength in old men and women. Suitable resistance training programs must be safe, effective and attractive for this cohort. However, the muscle size and strength adaptation to resistance training varies greatly in humans (24). Thus, the same type of resistance training might increase muscle function in some patients but might not have any measurable effect in others. In another study all subjects improved at least one measure of muscle size or function after 12-24 weeks of resistance exercise (9), suggesting that all subjects benefit from a suitably designed resistance training program.
2. Protein and other nutrients. The key "anabolic nutrient" is protein, which is digested into amino acids. Essential amino acids, and especially leucine, stimulate muscle protein syn-

thesis through mTOR, because the mTOR inhibitor rapamycin can block an amino acid-stimulated increase of human muscle protein synthesis (16). There is no conclusive evidence for an "anabolic window" during or around a bout of resistance exercise, but ingesting 20-40g of protein before, during and/or after resistance exercise should stimulate protein synthesis near-maximally (1, 42). The amount of protein ingested is more important than any potential effects of nutrition timing. Another question is "how much protein should older subjects consume per day?" Here, the Prot-Age study group recommends at least 1-1.2g per kg body weight per day and more for exercisers or those with chronic disease (4). Finally, what protein is best? Proteins with a high leucine content that are easily digested have the highest protein quality as measured by the digestible indispensable amino acid score (DIAAS). Whey and generally dairy proteins have high DIAAS scores (41) and are therefore especially recommended to promote muscle anabolism.

3. Other nutrients and ergogenic aids. Creatine, vitamin D supplements, ω-3 polyunsaturated fatty acids (PUFA, fish oil), or β-hydroxy-β-methylbutyrate (HMB), a leucine-related metabolite (29, 42) may all further enhance muscle anabolism.
4. Pharmaceutical treatments: In men, testosterone supplementation especially of hypergonadal men is an effective treatment to preserve muscle mass (49) but the side effects and the safety are insufficiently researched (18). β-agonists (33) as well as myostatin antibodies/inhibitors (5) can successfully be used to increase muscle size and function. These treatments might be used in cases where resistance exercise is impractical or ineffective or where maximal anabolism is needed, for example to treat hospitalized hip fracture patients.
5. Experimental treatments: Studies in mice have shown that the removal of senescent cells (2), or a short-term induction of the stem-cell inducing Yamanaka factors (39), can delay or reverse both organismal and skeletal muscle aging. Such interventions might become available for human treatment in the future (Fig. 2).

Summary and Conclusion

Societal aging is a major challenge for all societies affected by it. Financing societal aging and developing strategies to "rejuvenate" societies are two important tasks for governments. The third task is to keep the old population fit and healthy as this will ensure quality of life, keep the elderly out of hospitals, and care homes. Active living and endurance training programs are suited to achieve this goal but special interventions are required for those that have sarcopenia. For sarcopenic individuals it is important to utilize strategies that maintain or build muscle mass and improve muscle strength and power. Age-adapted, safe and attractive resistance exercise programs are the key focus in conjunction with ideally 20-40g of protein before, during or after a bout of exercise (the amount of protein is more important than the timing) and 1-1.2g per kg body weight per day.

However, a word of caution: whilst mTOR-mediated anabolism can increase muscle mass and size, there is evidence that high mTOR activity and more generally the promotion of anabolism over long periods reduces lifespan (23, 52, 55). Also surprisingly, long-term dietary restriction (which should inhibit mTOR, protein synthesis and muscle size) attenuates sarcopenia in rhesus monkeys (11). Therefore, whilst the activation of mTOR and protein synthesis stimulates muscle growth in the short term, decades of high mTOR activity may be detrimental for health, reduce lifespan and might even increase the risk of sarcopenia. Researchers should address this conundrum.

In addition to resistance exercise and protein, ergogenic aids such as creatine or vitamin D supplementation may be beneficial if there is e.g. a vitamin D deficiency or if a patient suffers from severe sarcopenia and frailty.

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I apologize to all the colleagues whose work I could not cite due to the word limit of this review. In addition, I would like to thank Claudia Schindler for proofreading this manuscript.

Dedication

This review is dedicated to the memory of Prof. Dr. Mike J. Rennie, an influential mentor of many scientists including myself and one of the pioneers and leaders in the field of human skeletal muscle aging. Prof. Mike J. Rennie passed away in January 2017.

Conflict of Interest

The authors have no conflict of interest.

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