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Aspects of physical medicine and rehabilitation in the treatment of deconditioned patients in the acute care setting: the role of skeletal muscle

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Summary Skeletal muscles are essential for movement as well as for survival. Knowledge about the organ skeletal muscle is underrepresented. Ageing and multiple chronic diseases are accompanied by loss of muscle mass, termed "muscle wasting". Nevertheless, muscles are one of the target organs within the rehabilitation process. This review highlights the role of skeletal muscles from various aspects, diagnostic procedures to quantify muscle mass and strength and, most importantly, lists countermeasures to muscle wasting. Although structured and progressive strength training is the cornerstone in the treatment of muscle wasting, several other methods exist to slow down or reverse the process of muscle wasting. Among them are neuromuscular electrical stimulation and alternative exercise modes, positioning, stretching and, as an emerging field, drug therapy.

Keywords Muscle wasting · Sarcopenia · Mechanisms · Prevention and treatment · Physical and rehabilitation medicine

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Aspekte der Physikalischen Medizin und Rehabilitation bei dekonditionierten Patienten im Akutkrankenhaus – die Rolle der Skeltetmuskulatur

Zusammenfassung Die Skelettmuskulatur ist nicht nur essentiell um Bewegungen auszuführen, sie ist auch entscheidend für das Überleben. Der Alterungsprozess sowie multiple chronische Erkrankungen führen zu einem Verlust an Muskelmasse, dem sogenannten „Muskelschwund". Der Muskel ist somit eines der Zielorgane im Rehabilitationsprozess. Diese Übersichtsarbeit beleuchtet die Rolle der Skelettmuskulatur aus verschiedenen Blickwinkeln. Diagnostische Verfahren zur Quantifizierung der Muskelmasse und -kraft sowie Maßnahmen, um dem Muskelschwund entgegenzuwirken, werden vorgestellt. Obwohl strukturiertes, progressives Krafttraining ein wichtiger Eckpfeiler in der Behandlung von Muskelschwund ist, existieren einige andere Methoden, die den Prozess des Abbaus der Muskulatur verringern oder rückgängig machen können. Dazu gehört die Neuromuskuläre Elektrostimulation genauso wie alternative Trainingsmodelle, die adäquate Lagerung des Patienten, Stretching oder, als aufkommendes Feld, die medikamentöse Therapie.

Schlüsselwörter Muskelschwund · Sarkopenie · Mechanismen · Prävention und Behandlung · Physikalische Medizin und Rehabilitation

Introduction

Skeletal muscle plays a key role in postural retention as well as locomotion for maintaining physical activities of human life. Skeletal muscle has a second role as an elaborate energy production and consumption system that influences the whole body's energy metabolism. A

third aspect emerges in recent years showing that skeletal muscles constitute a network for regulating the function of remote organs as well as skeletal muscle itself by the release of multiple types of myokines [1].

Skeletal muscle atrophy and loss of muscle performance are associated with acute and chronical illness such as sepsis, cancer, chronic heart failure, chronic kidney and chronic obstructive pulmonary disease (COPD). In the acute care setting, these conditions are quite common, and often patients have several problems simultaneously. Patients suffer from the imbalance between protein synthesis and protein degradation generated from inflammation, inactivity, malnutrition and the physiological process of ageing, which singularly or together lead to muscle atrophy.

Atrophied muscles generate less force and power, thus limiting an individual's functional performance. Besides these morphological changes, impairment of neural drive contributes to a decreased overall performance.

Up to date different terms like sarcopenia, myopenia, or muscle atrophy are common and confuse the reader. Therefore, recent work proposes the term "muscle wasting disease" and distinguishes between acute and chronic process [2].

This review reflects mechanisms of muscle wasting and its role in acute care setting conditions as well as therapeutic options to stop muscle atrophy and regain muscle mass, power and function.

Mechanisms of muscle wasting

Ageing-sarcopenia

The ageing process is associated with reduced type II muscle fibre size, increased adipose tissue accumulation around and between muscle fibres, lower fibre elasticity in both type I and IIA fibres, a reduction of maximum unloaded shortening velocity and a reduction in satellite cell number and activation [3, 4]. Reasons for this can be found in the loss of anabolic stimuli, a decline in the concentration of testosterone (and other anabolic hormones), higher concentrations of the messenger ribonucleic acid (RNA) and protein of inflammatory cytokines such as tumour necrosis factor (TNF)-alpha and the loss of the regenerative capacity of muscle fibres and increasing levels of myostatin, an inhibitor of myogenesis. Moreover, the concentration of myosin, the most important motor protein, has been shown to be reduced in fibres of old people [5]. Consequently, from the age of 50 the muscle mass decreases at an annual rate of 1–2 %, and a decline in muscle strength of 1,5–3 % per year is documented. As the level of physical activity declines too with increasing age, functional and clinical consequences are probable. Low Vitamin D and protein consumption work as cofactors. All this increases the risk to fall which leads to additional periods of immobility and ends up again in functional disabilities and muscle wasting. Today this phenomenon is described as sarcopenia, the loss of muscle mass and function with increasing age which finally leads to a loss of independence and quality of life of older people [6–8]. However, the ageing process is unfortunately inexorable, and in the acute care setting additional factors of muscle wasting have to be mentioned.

Immobility

Skeletal muscle atrophy occurs rapidly, no matter if it is generated from segmental or total immobility. Degradation processes primarily affect the muscle fibre cross-sectional area, whereas a decline of the number of muscle fibres cannot be shown in histological studies [9]. In the first 4 days of immobility most notably myofibrillar proteins are affected by the degradation process. After 9 days, both myofibrillar and sarcoplasmic proteins are reduced [10]. Additionally, immobilization leads to a reduction of neuronal activity and a shift from type I to type II fibres [11]. All this affects the muscles' function and can lead, for example, to a decline of range of movement (ROM) [12]. Microgravity mimics immobility and bed rest. Muscle composition after two weeks of spaceflight was altered but varied between individuals and muscle groups. The degree of atrophy appeared to be greater than that induced by 20 days of bed rest [13].

Acute critical illness

Rapid muscle atrophy in acute critical illness (e.g. sepsis and trauma), acute severe injury (e.g. burns) or systemic inflammation (e.g. in sepsis) causes a particularly rapid loss of skeletal muscle, which, in its most severe form, can lead to debilitating critical illness myopathy (CIM), also known as acute quadriplegic myopathy, acute care myopathy or critical care myopathy. This profound loss of muscle, which includes the loss of respiratory skeletal muscles, can lead to an inability to wean patients from mechanical ventilation and often ultimately to respiratory failure and death. Multiple factors may contribute to the rapid atrophy, including sepsis, inflammation, corticosteroids, inactivity, neuromuscular blocking agents, reduced caloric intake and insulin resistance. Moreover, histological analyses of muscle biopsies demonstrate three different patterns of atrophy in CIM: myopathy with abnormal variation in fibre size, fibre atrophy and single-fibre necrosis; thick-filament myopathy with selective loss of myosin (known as myosinopathy) [14], which may be associated with high-dose corticosteroid treatment and neuromuscular blocking agents and necrotizing myopathy with phagocytosis.

Chronic diseases

Muscle wasting is also a substantial component of many chronic diseases. As these conditions are often incurable, any therapies to prevent muscle loss and thus improve

the patients' quality of life would be highly beneficial. Patients with heart failure [15], chronic kidney disease (CKD) and COPD [16] exhibit profound muscle wasting that can deleteriously affect their prognosis. Despite the diverse nature of these diseases, they all seem to increase muscle proteolysis, primarily through the ubiquitin-proteasome system (UPS) 21 and the coordinated induction of atrogenes by forkhead box protein O (FOXO) transcription factors [17].

Chronic kidney disease

CKD can induce a catabolic state characterized by hypoalbuminemia and loss of muscle mass [18]. The metabolic acidosis that complicates renal injury stimulates muscle proteolysis through activation of the UPS. In addition, this increased proteolysis and rapid muscle loss requires glucocorticoids. It may be that apoptosis and caspase activation partially contribute to the muscle loss in CKD and other chronic conditions in which continued loss of cell proteins by atrogene induction may eventually lead to the activation of caspases. Fibre apoptosis has been observed during insect morphogenesis and in the muscles of aged sarcopenic animals, in which marked atrophy by the UPS precedes muscle apoptosis [19].

Chronic obstructive pulmonary disease

COPD is currently incurable and a major cause of morbidity and mortality worldwide, and skeletal muscle wasting is commonly observed in these patients [20]. Similar muscle wasting may also complicate other lung conditions, and muscle atrophy can be substantial in patients with pulmonary hypertension. Although muscle atrophy in lung disease can be caused by several mechanisms discussed above (i.e. sepsis, inflammation and reduced physical activity), other factors, especially hypoxia, may also contribute. The mechanism of hypoxia-induced muscle wasting is unknown, but some clinical studies have suggested that oxygen supplementation may improve muscle function [21].

Congestive cardiac failure

Patients with congestive cardiac failure often exhibit substantial skeletal muscle wasting, often termed cardiac cachexia. As in the other disease states discussed above, proteolysis by the UPS is activated, and myostatin–activin A signalling is increased. Myostatin is of particular interest in heart failure as, similar to skeletal muscle, cardiomyocytes express ActRIIB, the myostatin–activin A receptor [22].

Time response of muscle wasting in critical illness

In a study by Gruther et al., the time effect in immobilized intensive care patients on muscle wasting is shown by using ultrasound measurement [23]. Muscle layer thickness of the m. vastus intermedius and m. rectus femoris was measured at baseline and after 28 days of intensive care unit (ICU) stay. The results showed a significant negative correlation between muscle layer thickness and length of stay for both legs ($p < 0.01$).

Local muscle loss

Joint alterations lead subsequently to wasting of muscles surrounding the joint. After anterior cruciate ligament (ACL) reconstruction, substantial deficits were demonstrated for strength and cross-sectional area of the injured versus uninjured limb quadriceps muscles [24].

Molecular mechanisms similar to general muscle wasting in systemic diseases have been identified. In animal studies, quadriceps atrophy after ACL transection involves increased levels of myostatin, atrogin-1 and muscle ring finger 1 messenger ribonucleic acid (mRNA) and the accumulation of ubiquitinated protein [25]. Similar mechanisms were demonstrated in skeletal muscles adjacent to artificially induced joint inflammation [26].

Diagnosis

A consensus definition formulated by experts from a vast array of different medical fields recently suggested diagnosing sarcopenia when two criteria are fulfilled: (1) low muscle mass and (2) low gait speed [27]. Normal muscle mass is defined using data derived from young subjects aged 18–39 years from the Third National Health and Nutrition Examination Survey (NHANES) population [28], and the requirement for a diagnosis of sarcopenia is the presence of a muscle mass ≥ 2 standard deviations (SDs) below the mean of this reference population. This value can normally be calculated automatically by equipment such as dual energy X-ray absorptiometry (DEXA) scanners. A low gait speed is defined as a walking speed below 0.8 m/s in the 4-m walking test [29].

The European Working Group on Sarcopenia in Older People suggested diagnosing sarcopenia when at least two of three criteria apply: (1) low muscle mass, (2) low muscle strength and/or (3) low physical performance [30]. Cutoff points are defined in a similar manner as by the consensus group mentioned before, namely two SDs below the mean reference value for muscle mass and muscle strength of a reference population and a gait speed ≤ 0.8 m/s.

The close relationship between muscle mass and physical function is reflected by a concept of "sarcopenia with limited mobility" [31]. It defines a person with muscle loss whose walking speed is equal to or less than 1 m/s or who walks less than 400 m during a 6-min walk and

who has a lean appendicular mass corrected for height squared of two SDs or more below the mean of healthy persons between 20 and 30 years of age of the same ethnic group. However, these criteria remain cumbersome in daily clinical practice. Easily applicable tests such as handgrip strength testing or one of the biomarkers mentioned above may help to identify patients in need of a more thorough examination.

Biomarkers

A recent consensus statement acknowledges that the list of potential serum markers of sarcopenia is quite long [32]. It embraces markers of inflammation (e.g. C-reactive protein, interleukin-6 and TNF-alpha), clinical parameters, urinary creatinine, hormones (e.g. dehydroepiandrosterone sulphate, testosterone, insulin-like growth factor-1 (IGF-1) and vitamin D), products of oxidative damage or antioxidants. Since all the aforementioned markers are rather indirect measures of muscle loss, novel serum markers directly associated with changes in skeletal muscle mass and function are also promising. The one mentioned in the consensus statement is procollagen type III N-terminal peptide (P3NP). Another interesting marker in this regard is the C-terminal Agrin Fragment, a degeneration product of the neuromuscular junction [33].

Assessment of muscle mass

In the past, various methods for the quantification of total muscle mass and muscle mass of individual body segments were developed. Magnetic resonance tomography (MRT) and computed tomography (CT) still function as gold standard. Both, although expensive methods, enable the direct visualization of tissue and mathematical processing. Nevertheless, cheap and valid methods are needed to identify the wasting muscle.

Musculoskeletal ultrasound

With this method morphological parameters like maximal muscle thickness, pennation angle and echogenicity of the muscle can be measured. Usually images of musculus rectus femoris, musculus intermedius, musculus vastus lateralis and musculus vastus medialis are taken at 50 % of the thigh length from the greater trochanter to the lateral knee joint space. Pictures are made in the transverse and longitudinal plane. For further interpretation, images are downloaded and analysed with a special software program. Recent studies have shown that musculoskeletal ultrasound, especially of musculus vastus medialis, is a reliable method for monitoring muscle wasting [34]. In the acute care setting, the fact that measurements can be done at the bedside may be advantageous over other methods.

Bioelectrical impedance analysis

Bioelectrical impedance analysis (BIA) was developed for estimating body composition. Total body water, fat free mass, lean body mass, fat mass, body cell mass and extracellular mass can be measured. The measurement set-up is internationally standardized. With the constant signal of an alternating current of 0.8 mA at a frequency of 50 kHz, the impedance (resistance) of cellular tissue is measured. Janssen et al. showed that BIA is an effective method for the determination of skeletal muscle mass [35]. The relationship between MRI and BIA was investigated using a heterogeneous sample of 230 men and 158 women aged 18–86 years. A coefficient of determination of $R = 0.86$ and a standard error of mean of 2.7 kg or 9 % are shown.

Dual energy X-ray absorptiometry

While DEXA scans are used primarily to evaluate bone mineral density, it can also be used to measure body composition. DEXA is a widely available technology of low cost and provides valid estimates of skeletal muscle mass [36, 37]. If patients in the acute care setting need an exclusion from osteoporosis, DEXA is an appropriate method to measure the muscle mass along with it.

Assessment of muscle strength

Isometric maximum voluntary contraction force of the musculus quadriceps

For determining muscle strength of the musculus quadriceps, subjects are seated in an adjustable chair with their hips and their knees flexed at 90°. The pelvis and the thighs are secured, and an inflexible strap is placed around the ankle of the patient. Subjects are asked to cross their arms in front of the chest and to extend the leg as strongly as possible. The measurement is done three times for each leg with a resting period of 2 min. The best value of each leg is used for further evaluations. Assessment of the isometric maximum voluntary contraction (MVC) force of the musculus quadriceps is a valid tool to determine muscle strength of older people [38, 39].

Isokinetic dynamometry

With the isokinetic dynamometer, isokinetic peak torque of the knee extensors and flexors can be measured. Subjects are tested in a seated position with their hips flexed at 90°. The ankle of the tested leg is placed on a lever arm. The knee joint axis of rotation is aligned with the rotation axis of the machine. Subjects are securely strapped, allowing only knee flexion and extension. Two continuous maximal concentric knee extensions and flexions are

performed for peak torque measuring. The peak torque at different angular velocities can be measured.

Handgrip strength

Handgrip strength is measured with an isometric, hydraulic grip strength dynamometer. Subjects are seated to hold the dynamometer in the hand to be tested, with the elbow bent at an angle of 90° and the arm by the side of the body. Patients were encouraged to squeeze the dynamometer with maximum isometric effort, which is maintained for approximately 4–5 s. Three trials with a rest of 30 s between the tests were conducted for each hand alternately. Age- and sex-dependent normal values of grip strength are available [40]. Cutoff points for sarcopenia are defined as two SDs below the mean or 30 and 20 kg for men and women, respectively [41]. Measuring handgrip strength is a fast, easy and inexpensive way to measure muscle strength of the upper extremities. It is a reliable tool that shows a high correlation with quadriceps strength [42]. Because the handheld dynamometer is portable, it can be used very well for bedside testing.

Functionality

Gait speed

To calculate gait speed, subjects are instructed to walk 4 or 6 m at usual pace from a standing start. The average speed of two walks is measured with a clock and calculated in metres per second. Use of aids like walking frames or canes are allowed for this test. Large epidemiological studies confirmed the validity and sensitivity of this walking test even in older people [43, 44]. Gait speed is significantly associated with survival, while faster gait speeds than 0.8 m/s predict life expectancy beyond the median [45]. It is also a very important tool in the diagnostic algorithm of sarcopenia [32].

Timed Up-and-Go test

The Timed Up-and-Go test is a quick and easy tool to measure mobility, balance and risk of falls of elderly people. People are instructed to sit on a chair with an arm rest, stand up, walk a distance of 3 m, turn around, walk back and sit down. The time it takes to perform this is measured in seconds [46]. During the test the use of additives is allowed.

Interpretation: <10 s: normal mobility, 11–19 s: within normal limits for frail elderly and disabled patients, 20–29 s: the person needs assistance outdoors and further examination and intervention is indicated, >29 s: the person may be prone to falls. A time longer than or equal to a cutoff of 10.85 s on the Timed Up-and-Go test predicted sarcopenia with a sensitivity of 67 % and a specificity of 88.7 %. The accuracy of this cutoff for the Timed Up and Go test was good (0.80; 95% CI=0.66-0.94; p=0.002) [47].

Treatment strategies and promising agents

As common proteolytic pathways are activated during diverse types of atrophy, targeting certain key components of these common mechanisms is likely to be beneficial in many diseases. Currently, the only validated treatment is exercise, which reduces various types of atrophy and forms the mainstay of clinical management. However, exercise often is not a practical option for bedridden, frail, sarcopenic or older individuals, or those with acute illnesses. A primary effort must therefore be to prevent further muscle loss and regain or maintain basic locomotor functions ranging from ROM of joints to transfers in and out of bed and standing and walking. Nevertheless, verticalization of patients is a major step towards prevention of further muscle loss.

Positioning, passive stretching and passive movement

The ROM of a joint is crucial for its function. Is the joint moved to its limit, the muscle and its viscoelastic structures are stretched. Immobilization in contrast leads to muscle atrophy as well as a decline of ROM. In an animal study, the soleus muscle of rats was immobilized in the shortened position and subsequently stretched every 3 days for 40 min during 3 weeks. This resulted in reduced muscle atrophy compared to the immobilized, but unstretched, control group [12]. Furthermore, no decline of neuronal activity and protein levels of immobilized stretched muscles in rabbits was found [48]. In a patient study, critically ill patients who required a complete neuromuscular blockade for 7 days of ventilator support were treated with continuous passive motion (CPM) for three 3-h periods daily while the other leg served as control. Fibre area, fibre distribution and protein content were significantly less in the CPM limb [49].

Passive movement training resulted after 2 weeks in a twofold higher level of Ki-67 positive cells, co-localized with endothelial cells in the passively trained leg. It was paralleled by an increase in the number of capillaries around a fibre. After 4 weeks of training, capillary density was significantly higher than before training [50]. These findings imply that positioning and passive motion should have a place in the clinical management of immobilized patients.

Strength training

Adequate loading of skeletal muscles results in relevant and significant increases in muscle strength, muscle mass and functional ability. In acute care settings, these loading regimes often are neither suitable for acute and

critically ill patients nor feasible in clinical acute care settings. Therefore, different treatment strategies must be considered to initially improve patients' muscular conditions, and progression of activities must depend on patient tolerance and stability [51].

Neuromuscular electric stimulation

Electric current delivered by surface electrodes over skeletal muscles penetrates the skin and subcutaneous tissue, thus reaching the motor neurons. If current is delivered in short impulses of few microseconds, this sudden change of current leads to motor neuron depolarization and subsequently to muscle contractions. The parameters of the applied current determine the forms of muscle contraction. With greater pulse duration, more motor neurons are recruited, thus leading to greater muscle force/torque production. The amount of energy flowing per unit time affects the muscle response, that is higher intensity of current leads to increased excitability resulting in greater muscle torque/force. Furthermore, there is a direct inverse relationship to pulse duration, that is higher current requires shorter pulse duration to elicit similar muscle contractions. With increasing impulse frequency, levels overlapping action potential discharge before complete relaxation lead to summation (30–50 Hz) and to stronger muscle contractions. At very high frequencies above 50 Hz, the muscle will be in a state of tetany and remains contracted, which means the muscle will fatigue sooner [52].

A meta-analysis of 89 studies recommends a stimulation intensity of ≥ 50 % of maximal voluntary contraction, requesting a current intensity ≥ 50 mA, a stimulation frequency between 50 and 100 Hz, an impulse duration of 0.2–0.4 ms and a stimulation period of at least 4–6 weeks with a treatment frequency of three times per week, lasting 15 min per single session. The stimulation protocol should allow 3–10 s of muscle contraction with three times pause time corresponding to a 25 % duty cycle [53]. It has to be kept in mind that tissue impedance influences current flow towards motor neurons. In the presence of adiposis or edema, this means that higher pulse width is required to achieve adequate muscle contraction.

Neuromuscular electric stimulation (NMES) has shown to increase muscle force and muscle endurance [54, 55]. In acute postoperative conditions, it is an effective therapeutic option to prevent muscle wasting [56]. NMES application may be feasible in fully sedated patients on ICU wards. In an intra subject design, one leg was subjected to twice daily NMES of the quadriceps muscle for a period of 7 ± 1 days whereas the quadriceps muscle of the other leg acted as a non-stimulated control. NMES significantly increased mammalian target of rapamycin (mTOR) phosphorylation compared to baseline, with no changes in the control leg [57]. Similarly, a 4-day administration of NMES in postoperative patients after cancer surgery resulted in a significantly increased total mRNA content and conversely decreased ubiquitin-conjugated protein content and decreased proteasome activity as markers of the wasting pathway. Furthermore, higher currents induced higher mechano growth factor (MGF) mRNA levels in the NMES-treated muscles [56].

In elderly individuals, NMES was effective in improvement of muscle torque and functional performances and increased the size of fast muscle fibres. At molecular level, electric stimulation (ES) induced up-regulation of IGF-1 and modulation of Muscle-specific RING-finger protein 1 (MuRF-1), a muscle-specific atrophy-related gene. ES also induced up-regulation of relevant markers of differentiating satellite cells and of extracellular matrix remodelling, which might guarantee shape and mechanical forces of trained skeletal muscle as well as maintenance of satellite cell function [58].

Besides direct action on muscle fibres, NMES has been proven to elicit neural adaptions in a feed-back and feed-forward manner. NMES of finger extensors results in an MRI-proven activation of the contralateral primary motor cortex, primary sensory cortex and additional activation of the supplementary motor area [59]. Somatory networks are facilitated by NMES applications [60], thus contributing to motor relearning in bedridden patients.

Some authors showed a frequency-depending change in muscle fibre type and a different muscle output either towards increased strength and muscle mass [54], or improved endurance capacity (peak VO_2), resulting in increased myosin heavy chain isoforms and walking distance [55]. In healthy volunteers, NMES with a duration of 30 min can result in a substantial increase in oxygen uptake [61].

Considering safety aspects, clinical application of NMES in patients results in minor and clinically irrelevant alterations of the cardiovascular system [62, 63]. Under careful medical supervision, NMES of thigh muscles is applicable in the presence of cardiac pacemakers and even implanted defibrillators [64, 65].

Systematic reviews and meta-analysis prove the efficacy and effectiveness of this treatment concept (e.g. [66, 67]).

Resistance training

Progressive resistance training is a useful way to increase muscle strength, muscle mass and physical function of elderly and even frail people [68–71]. The American College of Sports Medicine summarized resistant training protocols for apparently healthy adults [72]. Based on the level of experience, different resistant training regimes are described focusing on exercise selection, one-repetition maximum (1RM), frequency, progression and age. For older people, 1–3 sets per exercise with 60–80 % of 1RM for 8–12 repetitions with 1–3 min of rest between sets for 2–3 days per week are recommended. It is important to maintain the training for several weeks. In a meta-analysis of Peterson et al., older people trained 12–24 weeks to improve muscle strength significantly [73].

Strength training programs with patients suffering from muscle wasting might differ from other training regimes. Because of the very low performance level of the muscle, single-set programs of up to 15 repetitions performed a minimum of 2 days × week (−1) may be appropriate. Each session should consist of 8–10 different exercises that train the major muscle groups. Single-set programs are less time-consuming and more cost-efficient, which generally translates into improved program compliance and furthermore produces most of the benefits of multiple-set programs. Patients with localized joint problems (e.g. osteoarthritis) may have to limit range of motion for some exercises and use lighter weights with more repetitions. Nevertheless, it is important to train until local muscle fatigue occurs [74]. Recently, the effectiveness of a slow movement and much reduced intensity of 30 % 1RM has been proven to increase muscle size and strength in older adults. The authors claim that the large total contraction time may be related to muscle hypertrophy and strength gain. A slow contraction, low-intensity training could be useful for preventing sarcopenia in older individuals [75].

Negative muscle work, for example eccentric muscle contractions, elicit hardly any load on cardiovascular and metabolic systems and are therefore well suited for initial strength training regimes in frail or severely ill subjects. Recent data suggest that eccentric lower extremity resistance exercise can improve muscle structure and function in those with limited exercise tolerance. The greater strength increase following negative work training resulted in improved balance and stair descent, and lower fall risk only in the treatment group. Because low energy cost is coupled to high force production with eccentric exercise, this intervention may be useful for a number of patients that are otherwise unable to achieve high muscle forces with traditional resistance exercise [76].

Attention should be paid to appropriate training equipment. It should be functional, secure and easy to use. Therefore, weight lifting machines where the weight and the individual's position can be adjusted easily and accurately are appropriate. The muscle contractions should be performed in concentric and eccentric actions with slow to moderate velocity. Since musculoskeletal injuries are the most common complications in strength training [77]. It is important to focus on learning the correct movement at the beginning of the training. Therefore, lower weights with a higher number of repetitions are recommended. A widely neglected area is easy accessibility and even wheelchair appropriate use of strength training machines. Future developments must consider these aspects to safely provide strength training to patients and frail elderly.

Elastic bands might be an alternative for weight training machines. They are highly accepted by older people and can be used at the bedside very early in the rehabilitation process. Therefore, it can be an effective tool of low cost. In a recent study by Oesen et al., 6 months of low-intensity resistance exercise training with older adults using elastic bands and their own body weight showed significant improvements in physical function of lower and upper extremities in comparison to a control group [78].

Aerobic exercise training

For previously sedentary persons, The American College of Sports Medicine requests 30–60 min of moderate exercise per day on 5–7 days per week (150 min per week). Exercise should involve major muscle groups and be continuous and rhythmic in nature. A gradual progression of exercise volume by adjusting exercise duration, frequency and/or intensity is essential. One (continuous) session or multiple sessions of >10 min are recommended. Light- to moderate-intensity exercise bouts of <10 min may be beneficial in very deconditioned individuals [72]. In healthy elderly individuals, exercise training has generally been shown to help maintain or improve muscle mass which is also associated with functional improvements in muscle strength and maximal aerobic capacity. Seventy-five-year-old adults performing a 12-week aerobic exercise training showed a higher quadriceps muscle volume paralleled with increased fibre cross-sectional area [79].

Whole-body vibration training

With this therapy, external mechanic vibration, usually over the soles of the feet, is transferred to the human body. There are two categories of swinging plates. One is swinging up and down and one side to side over a rocker in the middle. The hub is usually a few millimetres and should be adjustable, as well as the vibration frequency. From a vibration frequency of 12 Hz, the muscles can no longer compensate for the change in position triggered by the vibration. Though over the stretch reflex, muscle contractions occur. The clue is that 3 min of vibration at a frequency of 25 Hz have the same effect on the muscle as walking a distance of 4500 steps. Lam et al. showed in a review that a population of older people (64.3–81.9 years) significantly improved their Timed Up-and-Go performance [80], and a study by Zhang et al. showed for the first time significant improvements of muscle strength with whole-body vibration. Participants trained at a frequency of 6–26 Hz, 4–5 bouts × 60 s, 3–5 times weekly [81]. Whole-body vibration exercise can be used as a safe and effective method that can improve mobility, muscle strength, balance and the general health status of patients suffering from muscle wasting. In the acute care setting, innovative models are needed to apply vibration techniques to bedridden patients.

In clinical practice, training programs will be multimodal and adjusted to the patients' conditions. Progression of activities will be dependent on patient tolerance and stability [51].

Nutrition

As protein supplementation has been shown to improve muscle mass, strength and function in the elderly, its use in patients suffering from muscle wasting has been recommended by international bodies. The Society of Sarcopenia, Cachexia and Wasting Disease recommends a leucine-enriched essential amino acid intake between 1 and 1.5 g/kg/day to slow muscle loss [82]. Additionally, 700 IU of supplemental vitamin D per day are recommended [83]. Important to mention is that the supplemented protein is only transformed into musculature when the muscle sends the information that it is needed. Therefore, physical activity is a major precondition to apply protein supplements.

Drugs: future aspects

Although it is not the primary scope of this article, potential drug targets to block muscle wasting must be mentioned briefly.

Potential drug targets to block wasting

During exercise, several key factors that maintain skeletal muscle mass and promote hypertrophy are induced. The decrease in the levels of these proteins in various types of atrophy seems to contribute to the debilitating loss of muscle mass. Thus, agents that increase the levels of peroxisome-proliferator-activated receptor gamma coactivator 1- alpha (PGC1α), transcription factor JunB, or NAD-dependent protein deacetylase sirtuin 1 (SIRT1) could be of therapeutic benefit to slow muscle wasting in various catabolic states. There are several clinical trials on the way, none of them exceeding phase 2 as up to date. The following gives an overview on clinically relevant categories. For detailed information and an extensive overview see [84].

Myostatin and activin A antagonists

Myostatin is an autocrine factor that normally limits muscle size. Because of the growing evidence indicating that increased production of myostatin and its analogue, activin A, contribute to several forms of atrophy, inhibition of myostatin–activin A–growth differentiation factor 11 (GDF11) signalling is a promising therapy for multiple types of systemic wasting. Clinical phase 2 trials address a number of chronic conditions associated with muscle wasting, among them sarcopenia, cancer and COPD.

Insulin-like growth factor 1 analogous and grehlin

IGF-1 is a 7.5-kDa polypeptide that is structurally related to insulin. It is a circulating hormone secreted by the liver in response to pituitary growth hormone, but it is also an autocrine factor that is released by muscle fibres. IGF-1 stimulates protein synthesis, myoblast differentiation and muscle hypertrophy, and it inhibits protein degradation and many systemic forms of wasting. However, because of its rapid clearance, IGF-1 itself is not a suitable therapeutic agent. “Long-arginine” IGF-1 is a modified form of IGF-1 that has a long circulation time, binds to more tissue targets and is more potent than endogenous IGF-1. Its ability to induce nerve growth and promote myoblast proliferation offers greater therapeutic potential. However, several more potent variants have been developed that have prolonged circulation times and have reduced association with inhibitory IGF-1-binding proteins.

Beta2 adrenoreceptor agonists and phosphodiesterase inhibitors

Muscle growth can also be stimulated through activation of the G-protein-coupled β_2-adrenoreceptor, which causes cyclic adenosine monophosphate (cAMP) accumulation and protein kinase A activation, as well as by stimulating the protein synthesis (mTOR) pathway. Thus, β_2-adrenoreceptor agonists, in addition to stimulating the breakdown of glycogen and lipids, enhance protein synthesis, inhibit protein degradation and can reduce atrophy upon denervation, immobilization, cancer or ageing. In detail, clenbuterol decreased atrogene induction and proteolysis through both proteasomal degradation and autophagy. Presumably, the anabolic effects of adrenaline evolved as a physiological mechanism to maintain muscle mass in exercising or stressed individuals. Espindolol is a novel anabolic/catabolic-transforming agent that appears to possess three potential pharmacological targets in cancer cachexia: (1) reduced catabolism through nonselective b-blockade, (2) reduced fatigue and thermogenesis through antagonism of a subtype of 5-hydroxytryptamine receptor (5-HT1A), and (3) increased anabolism through partial b-2 receptor agonism [85].

Androgens and selective androgen receptor modulators

The androgenic steroid testosterone binds to nuclear receptors in muscle and increases protein synthesis and muscle mass. Despite this highly anabolic effects in humans, its clinical use is substantially limited by severe side effects, in particular the increased risk of developing prostate hypertrophy, cancer, masculinization and behavioural abnormalities. Therefore, non-steroidal selective androgen receptor modulators (SARMs) are being developed to overcome these issues. SARMs bind to the androgen receptor and display tissue-selective activation of androgenic signalling. SARMs cannot be metabolized into dihydrotestosterone or oestrogens, thus reducing the risk of developing prostatic hyperplasia. They seem to have promising therapeutic potential in various conditions, including cancer-associated cachexia, sarcopenia and osteoporosis, and in castrated

men after prostate surgery. Another novel anabolic agent has recently been tested in a randomized, double-blind, controlled trial.

Conflict of interest

The author declares that there are no actual or potential conflicts of interest in relation to this article.

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